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Role of Inflammation and Motility Disorders in the Development, Course and Consequences of Functional Gastrointestinal and Biliary Tract Diseases (Literature Review and Expert Panel Resolution)

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Aim: to present the results of the Expert Panel with a discussion of modern concepts of the pathogenesis of functional gastrointestinal diseases and the possibilities of multitarget therapy with trimebutine.
Key points. Low-grade inflammation can be considered as a morphological substrate of functional diseases with an increase in activated mastocytes and eosinophils, T-helpers 2 and T-helpers 17 in the gastrointestinal mucosa. In the development in the content of visceral hypersensitivity, the functional connection between mastocytes and TRPV1-positive sensory endings of the vagus nerve is of great importance. Proinflammatory cytokines and matrix metalloproteinases can enter the systemic circulation, provoking the development of systemic manifestations. Increased levels of proinflammatory cytokines are supported by altered intestinal permeability and microbiota. Functional diseases are believed to modify the symptoms and course of concomitant organic diseases of the gastrointestinal tract (for example, functional diseases of the biliary tract may contribute to the development of cholelithiasis, pancreatitis). The peripheral μ-, κ- and δ-receptor agonist trimebutine (Trimedat®) regulates the production of enterohormones, modulates motility throughout the gastrointestinal tract and normalizes visceral sensitivity. The effectiveness of trimebutine in the treatment of functional disorders has been shown in various studies. Trimebutine helps reduce the production of proinflammatory cytokines, including interleukin-6.
Conclusion. In the treatment of functional diseases of the gastrointestinal tract, trimebutine can be considered as a multitarget agent, since the drug helps to normalize motility, reduces the degree of visceral hypersensitivity, exhibits anti-inflammatory and neuroregenerative effects, and can also increase the effectiveness of treatment of concomitant diseases.
Keywords: functional gastrointestinal diseases, functional biliary tract diseases, low-grade inflammation, visceral hypersensitivity, motility, cytokines, trimebutine
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Роль воспаления и нарушений моторики в возникновении, течении и последствиях функциональных заболеваний желудочно-кишечного тракта и желчевыводящих путей (обзор литературы и резолюция Совета экспертов)

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Цель: представить итоги Совета экспертов с обсуждением современных представлений о патогенезе функциональных заболеваний желудочно-кишечного тракта и возможностей мультитаргетной терапии тримебутином.

Основные положения. Воспаление низкой степени можно рассматривать как морфологический субстрат функциональных заболеваний с повышением содержания в слизистой оболочке желудочно-кишечного тракта активированных мастоцитов и эозинофилов, Т-хелперов 2 и Т-хелперов 17. В развитии висцеральной гиперчувствительности большое значение придают функциональной связи между мастоцитами и TRPV1-позитивными сенсорными окончаниями блуждающего нерва. Провоспалительные цитокины и матриксные металлопротеиназы могут поступать в системную циркуляцию, провоцируя развитие системных проявлений. Повышенный уровень провоспалительных цитокинов поддерживают измененная кишечная проницаемость и микробиота. Функциональные заболевания, как предполагается, могут модифицировать симптоматику и течение сопутствующих органических заболеваний желудочно-кишечного тракта (например, функциональные заболевания билиарного тракта, возможно, способствуют развитию желчнокаменной болезни, панкреатита). Агонист периферических μ-, κ- и δ-рецепторов тримебутин (Тримедат®) регулирует выработку энтерогормонов, модулирует моторику на всем протяжении желудочно-кишечного тракта и нормализует висцеральную чувствительность. Эффективность тримебутина в лечении функциональных расстройств показана в различных исследованиях. Тримебутин способствует снижению продукции провоспалительных цитокинов, в том числе интерлейкина-6.

Заключение. В лечении функциональных заболеваний желудочно-кишечного тракта тримебутин можно рассматривать как средство мультитаргетного действия, так как препарат способствует нормализации моторики, уменьшает степень висцеральной гиперчувствительности, проявляет противовоспалительное и нейрорегенераторное действие, а также может повышать эффективность лечения сопутствующих заболеваний.

Ключевые слова: функциональные заболевания органов пищеварения, функциональные заболевания билиарного тракта, воспаление низкой степени, висцеральная гиперчувствительность, моторика, цитокины, тримебутин

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On May 28, 2024, the Expert Panel was held in Moscow to discuss the current understanding of the pathogenesis of functional gastrointestinal diseases and the possibilities of multitarget correction with trimebutine of the key pathogenesis components — motility disorders, visceral hypersensitivity and inflammation.

Functional gastrointestinal diseases are characterized by a high prevalence. In a 33-country study of more than 73,000 adults, criteria for at least one functional disease were identified in 40.3 % of those surveyed online and 20.7 % of those surveyed in person. Functional diseases of the digestive organs are 1.3–1.7 times more often diagnosed in women, reduce the quality of life, and increase the frequency of visits to the doctor [1].

Modern ideas about the pathogenesis of functional diseases imply impaired regulation along the "gastrointestinal tract — brain" axis. An important role is given to trigger factors — psychoemotional and physiological stress, genetic predisposition and external influences associated with an increased level of proinflammatory mediators in the mucous membrane. Low-grade inflammation can essentially be considered as the morphologic substrate of functional disease (Fig. 1). A number of features inherent in such an inflammatory process are distinguished: in a significant proportion of cases, an increased content of activated mast cells and eosinophils (not reaching the density

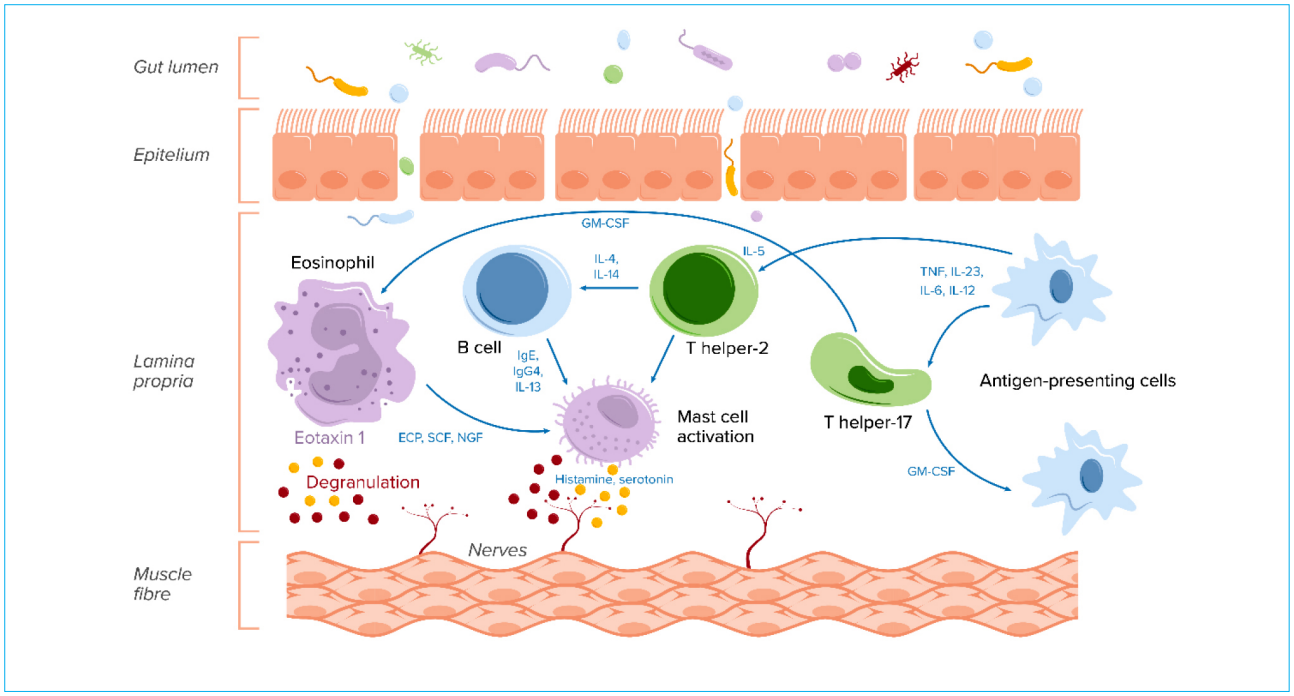

Figure 1. Schematic representation of disorders leading to the development of low-grade inflammation in the gastrointestinal mucosa in functional diseases of the digestive organs: GM-SCF — granulocyte-macrophage colony-stimulating factor; IL — interleukin; TNF — tumor necrosis factor; NGF — nerve growth factor; SCF — stem cell factor; ECP — eosinophil cationic protein; Ig — immunoglobulin

Рисунок 1. Схематическое изображение нарушений, приводящих к развитию воспаления низкой степени в слизистой оболочке желудочно-кишечного тракта при функциональных заболеваниях органов пищеварения: Gut lumen — Просвет кишечника; Epithelium — Эпителий; Lamina propria — Собственная пластинка слизистой оболочки; Muscle fiber — Мышечное волокно; Eosinophil — Эозинофил; GM-CSF — ГМ-КСФ (гранулоцитарно-макрофагальный колониестимулирующий фактор); IL — интерлейкин; TNF — фактор некроза опухоли; B-cell — B-лимфоцит; Ig — immunoglobulin; T helper 2 — T-хелпер-2; Mast cell activation — Активация мастоцитов; T helper 17 — T-хелпер-17; Antigen-presenting cells — Антиген-представляющие клетки; Eotaxin 1 — Эотаксин 1; ECP — эозинофильный катионный белок; SCF — фактор стволовых клеток; NGF — фактор роста нервов; Histamine, serotonin — Гистамин, серотонин; Degranulation — Дегрануляция; Nerves — Нервы

corresponding to eosinophilic inflammation and mastocytosis), as well as T-lymphocytes is noted; disruption of the integrity of intercellular contacts is characteristic. Similar changes are convincingly demonstrated in functional dyspepsia and irritable bowel syndrome with diarrhea (in the mucous membrane of the duodenum and colon, respectively). Data regarding the determination of the type of T-lymphocytes remain ambiguous, but it can be concluded that the overall picture corresponds to inflammation mediated by T-helpers 2 and 17 [2–5]. Moderately elevated calprotectin levels may be detected in patients' feces. Increased levels and activity of mast cells and T-lymphocytes have also been described in functional biliary tract diseases [6]. Due to the complexity of morphologic assessment of the state of the bile ducts, data on this problem are limited.

Under conditions of increased permeability of the epithelium and penetration of bacterial components and other lumenal antigens into the submucosal layer, activation of antigen-presenting cells with the secretion of proinflammatory cytokines and involvement of T-helpers 2 and 17, B-lymphocytes, and mastocytes is observed. T-helpers 17, through secretion of granulocyte-macrophage colony-stimulating factor, help maintain the activity of antigen-presenting cells and eosinophil recruitment. T-helpers 2 due to interleukin-4 (IL-4) secretion stimulate functional activity of B-lymphocytes, their transformation into plasmacytes and secretion of IgE, IgG4, IL-13 stimulating functional activity and degranulation of mastocytes. The content of mastocyte and eosinophil granules (histamine, serotonin, eotaxin-1, etc.) contribute to the maintenance of inflammation, the formation of visceral hypersensitivity and motor disorders (Fig. 1).

One of the central roles in the development of subclinical inflammation belongs to mastocytes.

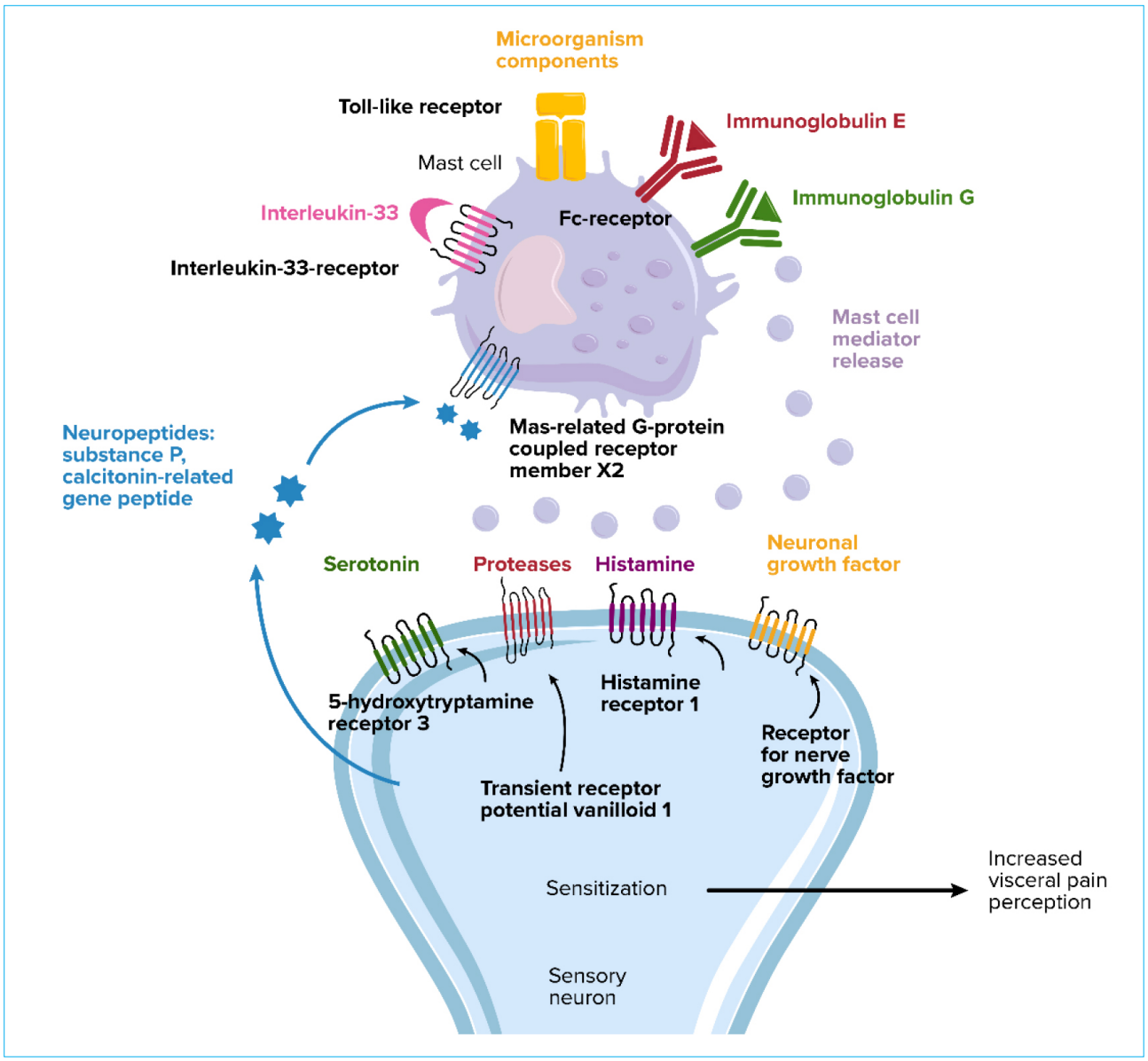

Figure 2. Mutual influence of capsaicin-sensitive neurons and mast cells, underlying the formation of visceral hypersensitivity and motor disorders. Substances released during partial degranulation of mast cells cause chronic excitation of neurons and changes in the functioning of neuroglia with the formation of visceral hypersensitivity, which is accompanied by the secretion of neurotransmitters that support the activation of mast cells

Рисунок 2. Взаимное влияние капсаицин-чувствительных нейронов и мастоцитов, лежащее в основе формирования висцеральной гиперчувствительности и нарушений моторики. Выделяющиеся при частичной дегранулляции мастоцитов вещества вызывают хроническое возбуждение нейронов и изменение работы нейроглии с формированием висцеральной гиперчувствительности, что сопровождается секрецией нейромедиаторов, поддерживающих активацию мастоцитов: Microorganism components — компоненты микроорганизмов; Toll-like receptor — толл-подобный рецептор; Immunoglobulin E — иммуноглобулин E; Mast cell — тучная клетка; Interleukin-33 — интерлейкин-33; Fc-receptor — рецептор для Fc-фрагмента иммуноглобулина; Immunoglobulin G — иммуноглобулин G; Interleukin-33-receptor — рецептор интерлейкина-33; Mast cell mediator release — высвобождение медиатора тучных клеток; Neuropeptides: substance P, calcitonin-related gene peptide — Нейропептиды: субстанция P, пептид гена, родственного кальцитонину; Mas-related G-protein coupled receptor member X2 — G-белок-сопряженный X2-рецептор, связанный с Mas-белком; Serotonin — серотонин; Proteases — протеазы; Histamine — гистамин; Neuronal growth factor — фактор роста нейронов; 5-hydroxytryptamine receptor 3 — серотониновый рецептор 3-го типа; Histamine receptor 1 — гистаминовый рецептор 1-го типа; Receptor for nerve growth factor — рецептор фактора роста нервов; Transient receptor potential vanilloid 1 — капсаициновый рецептор; Sensitization — сенсибилизация; Increased visceral pain perception — повышенное восприятие висцеральной боли; Sensory neuron — сенсорный нейрон

These cells express a variety of receptors — toll-like receptors (TLR), receptors to immunoglobulins E and G, complement components, Mas-related G-protein coupled receptor member X2 (MRGPRX2) and others. MRGPRX2 has been attributed a specific role in the pathogenesis of inflammation, visceral pain and motility disorders in functional digestive diseases. The receptor interacts with a variety of immune mediators (eosinophil proteins, proteases, defensins, etc.), neuropeptides (substance P, cortistatin, vasointegrin peptide, pituitary adenylate cyclase activating polypeptide), components contained in the lumen (pathogen-associated molecular pattern). Given the susceptibility of mastocytes to a variety of stimuli, it can be assumed that in the mucosa they act as "sensors" and simultaneously as "effectors" (along with neuroendocrine, bundle, dendritic and epithelial cells) [7]. The accumulation of mastocytes makes the gastrointestinal tract more susceptible to endogenous and intraluminal stimuli — microbial products and components, chemical constituents of food, stress, etc. Gastrointestinal mastocytes are in close contact with sensory endings of the vagus nerve expressing capsaicin receptors (TRPV1), and the functional relationship between them has been attributed great importance in the development of visceral hypersensitivity (Fig. 2) [8]. As part of low-grade inflammation, there is production of proinflammatory cytokines (IL-1β, -6, -8, tumor necrosis factor α (TNFα), interferon γ) and matrix metalloproteinases that can enter the systemic circulation. A significant increase in serum IL-6, -8, TNFα content has been shown in various variants of irritable bowel syndrome and functional constipation [9–11].

Cytokinemia is considered as a possible cause for the development of extraintestinal manifestations in functional diseases of the gastrointestinal tract. In particular, the content of proinflammatory cytokines has been shown to correlate with the impact of increased fatigue on the quality of life in irritable bowel syndrome (IBS) [12]. Under the influence of activated immune cells and cytokines produced by them, activation of afferent endings of the vagus nerve and microglia is observed; cytokines penetrate the blood-brain barrier. This influence causes functional changes in brain areas involved in emotion processing and mood regulation (insula, amygdala, ventral part of the corpus striatum, anterior cingulate cortex, prefrontal cortex). All these data indicate the systemic nature of inflammation in functional diseases [3, 13].

Increased intestinal permeability, changes in the intestinal microbiota (in particular, increased population of *Bacteroidetes* spp.) and excessive bacterial growth, which are significantly more frequently detected in patients with functional digestive diseases, play an undoubted role in the maintenance of low-grade inflammation [13, 14].

In about 30 % of cases, there is a combination of functional gastrointestinal diseases. The most characteristic combination is functional dyspepsia (FD) and IBS: among patients with FD, the prevalence of IBS ranges from 13 % to 46 % and is, on average, 8 times higher compared to the population; 42–87 % of patients with IBS have diagnostic criteria for FD at the same time. Almost half of patients with IBS have biliary motor dysfunction. In case of combination, the number and severity of symptoms are significantly higher, and the associated autonomic and psychoemotional disturbances are more pronounced [15]. The combination of FD, IBS and functional biliary disorders with heartburn, gastroesophageal reflux disease is also very characteristic [16]. The basis for this, apparently, are motility disorders with retrograde reflux of luminal contents — gastroesophageal and duodenogastric reflux, malfunction of natural clearance of the gastrointestinal tract.

Pathogenesis of functional diseases of the biliary tract has its own peculiarities: lithogenicity of bile, changes in contractile function of the gallbladder and biliary sphincters play a major role in their development. The result can be an altered response of smooth muscle cells to cholecystokinin and impaired relaxation of the sphincters and emptying of the gallbladder, as well as increased secretion of mucin and the formation of bile crystals and microliths, which contribute to the development of chronic inflammation. Under these conditions, visceral hypersensitivity is formed and myocyte response to cholecystokinin is impaired [17, 18].

Of great scientific and practical interest is the opinion that there may be a sequence of events in which gallbladder dysfunction and, presumably, concurrent sphincter of Oddi dysfunction predispose to the development of cholelithiasis (Fig. 3). After cholecystectomy, persistent or newly formed dysfunction of the sphincter of Oddi is the cause of biliary pain episodes, representing one of the variants of situations when the patient is diagnosed with postcholecystectomy syndrome. However, it is advisable to avoid such a general wording of the diagnosis; it is necessary to establish the specific cause of the symptoms present — postoperative complication, dysfunction of the sphincter of Oddi or other functional disease, recurrence of stone formation, etc.

In Russia, about 200,000 cholecystectomies are performed annually. Gallbladder removal does not compensate for the complex pathophysiologic

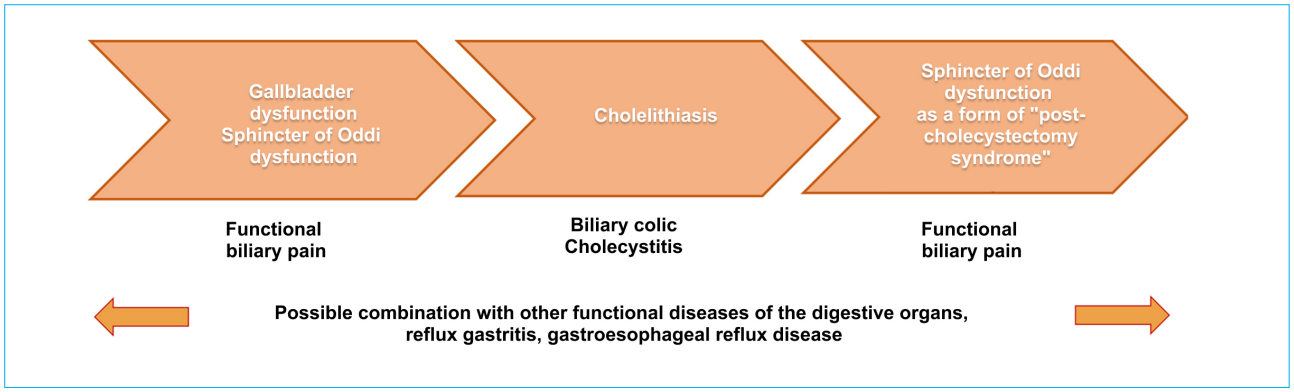

Figure 3. A sequence of events reflecting the progression of functional biliary disorder with the addition of organic changes

Рисунок 3. Последовательность событий, отражающая прогрессирование функционального билиарного расстройства с присоединением органических изменений: Gallbladder dysfunction, Sphincter of Oddi dysfunction — дисфункция желчного пузыря, дисфункция сфинктера Одди; Cholelithiasis — желчнокаменная болезнь; Sphincter of Oddi disfunction as a form of "postcholecystectomy syndrome" — дисфункция сфинктера Одди как форма «постхолецистэктомического синдрома»; Functional biliary pain — функциональная билиарная боль; Biliary colic, Cholecystitis — желчная колика, холецистит; Possible combination with other functional diseases of the digestive organs, reflux gastritis, gastroesophageal reflux disease — возможно сочетание с другими функциональными заболеваниями органов пищеварения, рефлюкс-гастритом, гастроэзофагеальной рефлюксной болезнью

abnormalities underlying the development of cholelithiasis. Up to 50 % of patients in different terms after cholecystectomy complain of abdominal pain, unstable stools, flatulence. In half of the cases, these symptoms are due to pre-existing functional diseases (FD and IBS) and are also associated with sphincter of Oddi dysfunction [19]. More than 80 % of patients both at the stage of gallbladder dysfunction and after cholecystectomy have gastric and/or duodenal motility disorders. Almost all patients with sphincter of Oddi dysfunction after cholecystectomy show signs of decreased duodenal motility, half of them have duodenogastric reflux; microscopic signs of inflammation, cholesterosis, muscle hypertrophy, fibrosis and adenomyomatosis are found in papillary tissue samples in more than half of cases [18].

Functional diseases of the gastrointestinal and biliary tract may contribute to the development of chronic pancreatitis. Pancreatic sphincter of Oddi dysfunction increases the risk of acute pancreatitis attacks. The trigger mechanism of biliary pancreatitis development is pressure increase in the ductal system, which can be caused by functional causes — dyssynergy of the sphincter apparatus of the distal biliary tracts and the main pancreatic duct, hypertonus of the sphincter of Oddi [20]. Biliary motility disorders prevent timely and full flow of bile and pancreatic juice into the duodenum. Slow motility (e.g., gastro- or duodenostasis) contributes to impaired mixing of enzymes with chyme, whereas rapid transit of intestinal contents is accompanied by a decrease in enzyme concentration as a result of dilution [21]. On the other hand, the influence of external pancreatic secretion (enzymes and bicarbonates) on the gastrointestinal tract is relevant. Disruption of secretion may contribute to the development of functional gastrointestinal disorders [22].

Subclinical systemic inflammation not only serves as a basis for the development of gastrointestinal clinical symptoms — epigastric pain, postprandial distress syndrome, intestinal motility disorders, biliary pain, but probably can contribute to the addition of extraintestinal manifestations — asthenia, migraine, headache, reduces the quality of life of patients [23].

A number of experts consider methods of influencing low-grade inflammation in the mucous membrane as one of the promising areas of treatment for functional diseases of the gastrointestinal and biliary tract [11].

Trimebutine is widely used for the treatment of functional diseases of the gastrointestinal and biliary tract. This drug exhibits agonist properties of peripheral μ-, κ- and δ-receptors and does not pass through the blood-brain barrier into the central nervous system. Trimebutine stimulates the release of motilin and regulates the production of other enterohormones — vasoactive intestinal peptide, gastrin and glucagon. Trimebutine stimulates gastric emptying, induces phase III of the migratory motor complex in the intestine and normalizes contractile activity of the colon. Due to some multidirectional effect of stimulation of μ-,

Table. Results of studies of the drug Trimedat® in functional gastrointestinal disorders
Таблица. Результаты исследований препарата Тримедат® при функциональных гастроэнтерологических расстройствах

Reference *Источник*	FD group *Группа ФР*	*n*	Results *Результаты*
Kardasheva S.S., et al., 2018 [29] *Кардашева С.С. и др., 2018 [29]*	FD / *ФД*	100	Reduction in the severity of the main symptoms and a significant increase in the quality of life *Уменьшение выраженности основных симптомов и достоверное повышение качества жизни*
Kountouras J., et al., 2020 [30]		185	Decreased symptom severity according to the GDSS questionnaire, increased gastric emptying rate *Уменьшение тяжести симптомов по опроснику GDSS, увеличение скорости опорожнения желудка*
Young Y.J., et al., 2017 [31]		4473	Higher efficacy than itopride and acotiamide and the same as domperidone and metoclopramide, but unlike the latter, trimebutine is suitable for course administration *Более высокая эффективность, чем у итоприда и акотиамида, и такая же, как у домперидона и метоклопрамида, но, в отличие от последних, тримебутин подходит для курсового приема*
Svistunov A.A., et al., 2018 [32] *Свистунов А.А. и др., 2018 [32]*	Gallbladder and sphincter of Oddi dysfunction *Дисфункция желчного пузыря и сфинктера Одди*	85	Statistically significant normalization of the contractile-evacuation function of the gallbladder and sphincter of Oddi *Статистически значимая нормализация сократительно-эвакуаторной функции желчного пузыря и сфинктера Одди*
Ivashkin V.T., et al., 2018 [33] *Ивашкин В.Т. и др., 2018 [33]*		100	Reducing the severity of biliary pain, nausea, bloating *Уменьшение тяжести билиарной боли, тошноты, вздутия живота*
Yakovenko E.P., et al., 2014 [34] *Яковенко Э.П. и др., 2014 [34]*		96	Clinical remission in 96 % of patients, which was maintained in 94 % of them for at least 1 month after drug discontinuation *Клиническая ремиссия у 96 % пациентов, которая сохранялась у 94 % из них в течение не менее 1 мес. после отмены препарата*
Vitton V., et al., 2008 [35]		59	Treatment with trimebutine + nitrates on demand allowed 77 % of patients to avoid sphincterotomy *Терапия тримебутином + нитраты по требованию позволила 77 % пациентов избежать выполнения сфинктеротомии*
Andreev D.N., et al., 2021 [36] *Андреев Д.Н. и др., 2021 [36]*	FD, IBS, biliary dysfunction, sphincter of Oddi dysfunction *ФД, СРК, дисфункция желчевыводящих путей, дисфункция сфинктера Одди*	3831	Relief of pain/burning sensation in the epigastric region, biliary pain, feeling of fullness in the stomach and early satiety/feeling of heaviness, heartburn, belching, bloating, bowel disorders (constipation, diarrhea, their alternation) *Купирование боли / чувства жжения в эпигастральной области, билиарной боли, чувства переполнения желудка и раннего насыщения /чувства тяжести, изжоги, отрыжки, вздутия живота, нарушений стула (запор, диарея, их чередование)*
Ruepert L., et al., 2011 [25]	IBS / *СРК*	1392	Superior to placebo in relieving/ relieving abdominal pain *Превосходит плацебо в купировании/ облегчении боли в животе*

Note: FD — functional disorders, FD — functional dyspepsia, IBS — irritable bowel syndrome, *n* — number of patients.
Примечание: ФР — функциональные расстройства, ФД — функциональная диспепсия, СРК — синдром раздраженного кишечника, *n* — число пациентов.

κ- and δ-receptors, trimebutine modulates motility throughout the gastrointestinal tract and biliary tract, normalizes visceral sensitivity [24]. The efficacy of trimebutine in the treatment of IBS was confirmed in a 2011 Cochrane Library meta-analysis [25]. The results of another meta-analysis of clinical trials showed that the difference between trimebutine at therapeutic doses and placebo with regard to adverse events was not statistically significant [26]. In both functional and organic diseases with spastic pain, trimebutine (Trimedat®) showed greater efficacy than other antispasmodics not only in terms of gastrointestinal symptoms but also in terms of improved quality of life (Table) [27, 28].

In recent years, evidence has emerged that the therapeutic potential of trimebutine has not yet been fully understood. Trimebutine exhibits anti-inflammatory activity by inhibiting the production of pro-inflammatory cytokines, including IL-6 (Fig. 4). The anti-inflammatory effects of trimebutine have been demonstrated in experiments. Trimebutine pretreated macrophages produced less IL-6 under conditions of endotoxin stimulation. Administration of trimebutine to mice with experimental sepsis induced by endotoxin improved their survival [37]. The drug blocks common intracellular components of three signaling cascades. The first cascade is associated with the activation of the RAGE ectodomain involved in the development of inflammation under the influence of a variety of stimuli. The second is with the activation of TLR4 under the action of lipopolysaccharide of gram-negative bacteria. The third is with the activation of TLR2 under the influence of components of gram-positive bacteria. Trimebutine blocks IRAK1 and ERK1/2 molecules and the subsequent activation of JNK and κB nuclear factor. As a consequence, the proinflammatory signal is not transmitted to the cell nucleus and the production of proinflammatory cytokines does not occur. Moreover, trimebutine blocks TLR-7/8/9, which interact with microbial RNAs and are involved in endosome formation.

The combination of antispasmodic, prokinetic, analgesic and anti-inflammatory action make

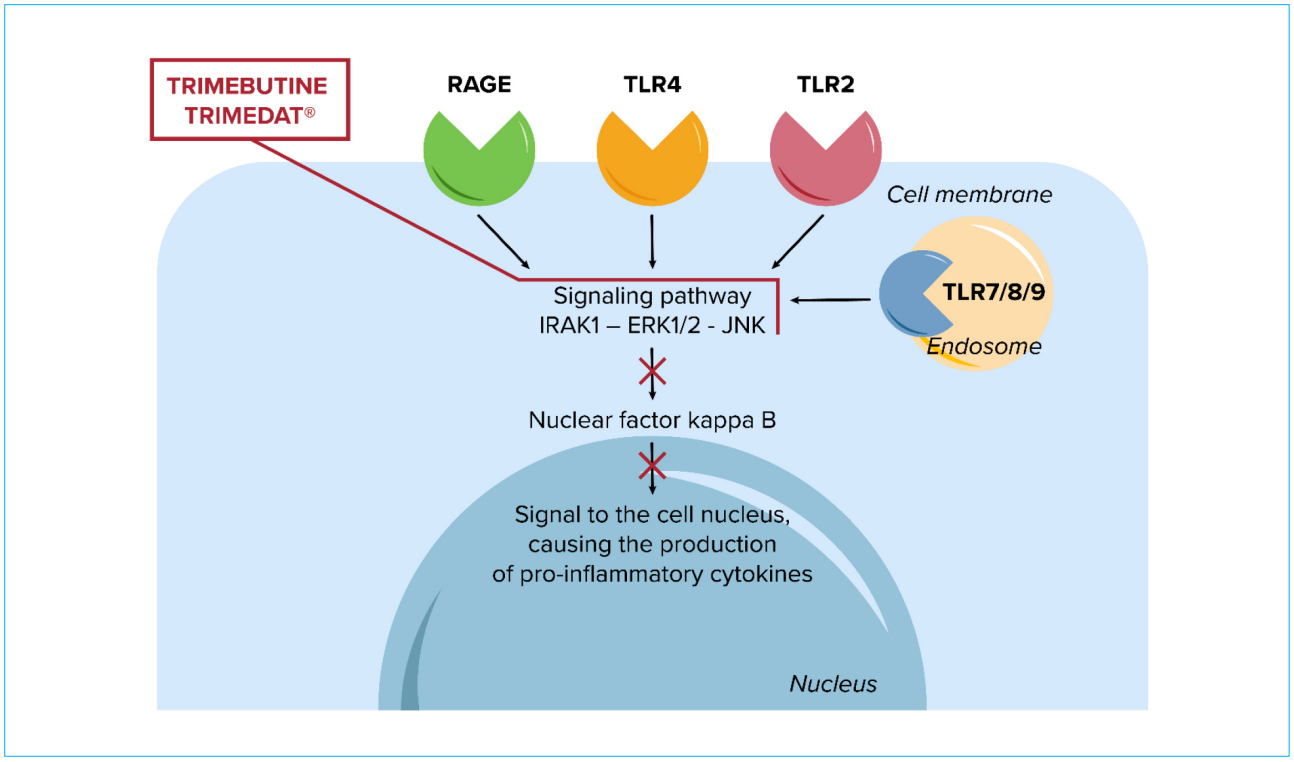

Figure 4. Mechanisms of the anti-inflammatory action of trimebutine: RAGE — receptor for advanced glycation end products; TLR — toll-like receptor; IRAK1 — Interleukin-1 receptor-associated kinase 1; ERK — extracellular signal-regulated kinase; JNK — c-Jun N-terminal kinase

Рисунок 4. Механизмы противовоспалительного действия тримебутина: RAGE — рецептор конечных продуктов гликирования; TLR — толл-подобный рецептор; Cell membrane — мембрана клетки; Signalling pathway — сигнальный каскад; IRAK1 — киназа, ассоциированная с рецептором интерлейкина-1; киназа, регулируемая внеклеточным сигналом; JNK— c-Jun N-концевая киназа; Nuclear factor κB — Ядерный фактор κB; Signal to the cell nucleus, causing the production of proinflammatory cytokines — Сигнал к ядру клетки, вызывающий выработку провоспалительных цитокинов; Cell nucleus — ядро клетки

trimebutine (Trimedat®) a multitarget product due to its effect on all key pathophysiological components of functional diseases of the gastrointestinal and biliary tract.

Trimedat® is the most studied product of trimebutine in the Russian Federation (Table). In a number of works of the past years, anti-inflammatory effect of Trimedat® was already noted, in particular, in patients with IBS along with pain reduction, after a 4-week administration normalization of calprotectin activity in feces was observed [38]. Interestingly, even in ulcerative colitis trimebutine has a marked anti-inflammatory effect: the addition of the product to mesalazine in the treatment of patients with ulcerative colitis for 8 weeks resulted in a more pronounced decrease in the level of proinflammatory cytokines — TNFα and IL-23, as well as in serum ESR and D-dimer, which allowed to achieve a more pronounced clinical effect [39]. In addition to anti-inflammatory activity, the neuroregenerative potential of trimebutine has recently been described. In experimental spinal cord injury in mice, the use of trimebutine was accompanied by a decrease in the severity of glial scarring and enhanced regenerative growth of axons, improved recovery of locomotor function [40]. Thus, the fact that Trimedat® has, in addition to its antispasmodic, prokinetic and analgesic, anti-inflammatory and neuroregenerative mechanisms of action, allows it to affect deeper links in the pathogenesis of functional diseases of the gastrointestinal and biliary tract and makes it easier for the doctor to select drug therapy, while simultaneously reducing the drug burden on the patient [41]. New data present Trimedat® as a versatile multi-target motility regulator with analgesic and anti-inflammatory effects. Patients reported relief of symptoms as early as 20 minutes after trimebutine administration [42].

Treatment of functional biliary disorders represents a special area of Trimedat® use. Given the close relationship between the function of the biliary system and the state of the stomach and duodenum, elements of the prokinetic effect of trimebutine may be particularly useful. Trimebutine is one of the few products (along with nifedipine, phosphodiesterase type IV inhibitors, hyoscine butyl bromide, octreotide, and nitrates) included in clinical guidelines for the treatment of sphincter of Oddi dysfunction. Trimebutine is a drug for which there is rigorous evidence-based data on efficacy in the treatment of sphincter of Oddi dysfunction [21]. 77 % of patients with sphincter of Oddi dysfunction after cholecystectomy avoided sphincterotomy while taking trimebutine and nitrates [35]. Trimedat® can be classified as the product of choice for the treatment of gallbladder and sphincter of Oddi dysfunction, which has been demonstrated in various studies involving more than 1000 patients [32–34].

The normalizing effect of trimebutine on gastrointestinal motility throughout the gastrointestinal tract and the anti-inflammatory effect of Trimedat® explain its positive effect on symptoms of gastro-esophageal and duodenogastric reflux [43, 44]. A meta-analysis of clinical trials showed that trimebutine is more effective than itopride and acotiamide in the treatment of functional dyspepsia and as effective as domperidone and metoclopramide, but unlike the latter, it is suitable for course administration [31].

Resolution of the Expert Panel

1. Low-grade inflammation associated with the development of visceral hypersensitivity and impaired motility plays a significant role in the pathogenesis of functional gastrointestinal diseases. The features that characterize such inflammation include an increased content of activated mast cells and eosinophils, T-helpers 2 and T-helpers 17 against the background of decreased permeability of the epithelial barrier.

2. The entry of proinflammatory mediators into the blood in functional gastrointestinal diseases can contribute to the development of extraintestinal symptoms, including those from the central nervous system (asthenia, headache).

3. Common mechanisms of the pathogenesis of functional gastrointestinal disorders serve as the basis for the frequent combination of various functional diseases in one patient.

4. Functional diseases of the biliary tract may contribute to the development of organic lesions (cholelithiasis, recurrent acute, chronic pancreatitis) or aggravate the course of concomitant organic diseases of the gastrointestinal tract (for example, contributing to the development of secondary exocrine pancreatic insufficiency in patients with chronic pancreatitis).

5. Trimedat® has a multitarget effect on the main pathophysiological links of functional disorders of the gastrointestinal tract due to the normalization of motility and visceral sensitivity and due to the anti-inflammatory effect, which contributes to the complete elimination of symptoms and the achievement of stable remission in irritable bowel syndrome, functional dyspepsia, dysfunction of the gallbladder and sphincter of Oddi and their combination.

6. Further studies of the anti-inflammatory and neuroregenerative effect of Trimedat® in functional disorders of the gastrointestinal tract are advisable.

References / Литература

1. *Sperber A.D., Bangdiwala S.I., Drossman D.A., Ghoshal U.C., Simren M., Tack J., et al.* Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. *Gastroenterology*. 2021;160(1):99–114.e3. DOI: 10.1053/j.gastro.2020.04.014
2. *Силаева А.С., Буеверова Е.Л., Шульпекова Ю.О.* Дуоденальная эозинофилия при функциональной диспепсии. *Российский журнал гастроэнтерологии, гепатологии, колопроктологии.* 2023;33(2):87–94. [*Silaeva A.S., Bueverova E.L., Shulpekova Yu.O.* Duodenal eosinophilia in functional dyspepsia. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2023;33(2):87–94. (In Russ.)]. DOI: 10.22416/1382-4376-2023-33-2-87-94
3. *Burns G., Carroll G., Mathe A., Horvat J., Foster P., Walker M.M., et al.* Evidence for local and systemic immune activation in functional dyspepsia and the irritable bowel syndrome: A systematic review. *Am J Gastroenterol*. 2019;114(3):429–36. DOI: 10.1038/s41395-018-0377-0
4. *Wouters M.M., Vicario M., Santos J.* The role of mast cells in functional GI disorders. *Gut*. 2016;65(1):155–68. DOI: 10.1136/gutjnl-2015-309151
5. *Burns G.L., Bruce J.K., Minahan K., Mathe A., Fairlie T., Cameron R., et al.* Type 2 and type 17 effector cells are increased in the duodenal mucosa but not peripheral blood of patients with functional dyspepsia. *Front Immunol*. 2023:13:1051632. DOI: 10.3389/fimmu.2022.1051632
6. *Arshi J., Layfield L.J., Esebua M.* Mast cell infiltration and activation in the gallbladder wall: Implications for the pathogenesis of functional gallbladder disorder in adult patients. *Ann Diagn Pathol*. 2021;54:151798. DOI: 10.1016/j.anndiagpath.2021.151798
7. *Oshima T.* Functional dyspepsia: Current understanding and future perspective. *Digestion*. 2024;105(1):26–33. DOI: 10.1159/000532082
8. *Defaye M., Abdullah N.S., Iftinca M., Hassan A., Agosti F., Zhang Z., et al.* Gut-innervating TRPV1+ neurons drive chronic visceral pain via microglial P2Y12 receptor. *Cell Mol Gastroenterol Hepatol*. 2022;13(4):977–99. DOI: 10.1016/j.jcmgh.2021.12.012
9. *Seyedmirzaee S., Hayatbakhsh M.M., Ahmadi B., Baniasadi N., Bagheri Rafsanjani A.M., Nikpoor A.R., et al.* Serum immune biomarkers in irritable bowel syndrome. *Clin Res Hepatol Gastroenterol*. 2016;40(5):631–7. DOI: 10.1016/j.clinre.2015.12.013
10. *Mokhtare M., Alimoradzadeh R., Agah S., Mirmiranpour H., Khodabandehloo N.* The association between modulating inflammatory cytokines and constipation of geriatrics in Iran. *Middle East J Dig Dis*. 2017;9(4):228–34. DOI: 10.15171/mejdd.2017.78
11. *Kumar S., Singh P., Kumar A.* Targeted therapy of irritable bowel syndrome with anti-inflammatory cytokines. *Clin J Gastroenterol*. 2022;15(1):1–10. DOI: 10.1007/s12328-021-01555-8
12. *Norlin A.K., Walter S., Icenhour A., Keita A.V., Elsenbruch S., Bednarska O., et al.* Fatigue in irritable bowel syndrome is associated with plasma levels of TNF-alpha and mesocorticolimbic connectivity. *Brain Behav Immun*. 2021;92:211–22. DOI: 10.1016/j.bbi.2020.11.035
13. *Šojat D., Volarić M., Keškić T., Volarić N., Cerovečki V., Trtica Majnarić L.* Putting functional gastrointestinal disorders within the spectrum of inflammatory disorders can improve classification and diagnostics of these disorders. *Biomedicines*. 2024;12(3):702. DOI: 10.3390/biomedicines12030702
14. *Wei L., Singh R., Ro S., Ghoshal U.C.* Gut microbiota dysbiosis in functional gastrointestinal disorders: Underpinning the symptoms and pathophysiology. *JGH Open*. 2021;5(9):976–87. DOI: 10.1002/jgh3.12528
15. *Мехтиев С.Н., Мехтиева О.А., Берко О.М.* Синдром перекреста функциональных гастроинтестинальных расстройств: общие механизмы патогенеза как ключ к рациональной терапии. *Российский журнал гастроэнтерологии, гепатологии, колопроктологии*. 2022;32(4):95–103. [*Mekhdiyev S.N., Mekhdieva O.A., Berko O.M.* Overlap of functional gastrointestinal disorders: Common mechanisms of pathogenesis as a key to rational therapy. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2022;32(4):95–103. (In Russ.)]. DOI: 10.22416/1382-4376-2022-32-4-95-103
16. *Lee S.W., Chang C.S.* Impact of overlapping functional gastrointestinal disorders on the quality of life in patients with gastroesophageal reflux disease. *J Neurogastroenterol Motil*. 2021;27(2):176–84. DOI: 10.5056/jnm19006
17. *Simon D.A., Friesen C.A., Schurman J.V., Colombo J.M.* Biliary dyskinesia in children and adolescents: A mini review. *Front Pediatr*. 2020;8:122. DOI: 10.3389/fped.2020.00122
18. *Ивашкин В.Т., Маев И.В., Шульпекова Ю.О., Баранская Е.К., Охлобыстин А.В., Трухманов А.С. и др.* Клинические рекомендации Российской гастроэнтерологической ассоциации по диагностике и лечению дискинезии желчевыводящих путей. *Российский журнал гастроэнтерологии, гепатологии, колопроктологии*. 2018;28(3):63–80. [*Ivashkin V.T., Mayev I.V., Shulpekova Yu.O., Baranskaya Ye.K., Okhlobystin A.V., Trukhmanov A.S., et al.* Diagnostics and treatment of biliary dyskinesia: Clinical guidelines of the Russian gastroenterological Association. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2018;28(3):63–80. (In Russ.)]. DOI: 10.22416/1382-4376-2018-28-3-63-80
19. *Кучерявый Ю.А.* Боль и диспепсия после холецистэктомии. *Доктор.Ру. Гастроэнтерология*. 2016;118(1):27–32. [*Kutcheryavy Yu.A.* Pain and dyspepsia following cholecystectomy. *Doctor.Ru. Gastroenterology*. 2016;118(1):27–32. (In Russ.)].
20. *Ильченко А.А.* Билиарный панкреатит. *РМЖ*. 2012;20(15):803. [Ilchenko A.A. Biliary pancreatitis. *Russian Medical Journal*. 2012;20(15):803. (In Russ.)].
21. *Cotton P.B., Elta G.H., Carter C.R., Pasricha P.J., Corazziari E.S.* Rome IV. Gallbladder and sphincter of Oddi disorders. *Gastroenterology*. 2016:S0016-5085(16)00224-9. DOI: 10.1053/j.gastro.2016.02.033
22. *Futagami S., Wakabayashi M.* Pancreatic dysfunction and duodenal inflammatory responses coordinate with refractory epigastric pain including functional dyspepsia: A narrative review. *J Nippon Med Sch*. 2022;89(3):255–62. DOI: 10.1272/jnms.JNMS.2022_89-311
23. *Zanchi C., Pintaldi S., Di Leo G., Ronfani L., Zamagni G., Viel M., et al.* Fifteen-years follow-up in a cohort of children with functional gastrointestinal disorders: Prevalence and risk factors to develop neuropsychiatric disorders and other comorbidities. *Children (Basel)*. 2021;8(10):838. DOI: 10.3390/children8100838
24. *Delvaux M., Wingate D.* Trimebutine: Mechanism of action, effects on gastrointestinal function and clinical results. *J Int Med Res*. 1997;25(5):225–46. DOI: 10.1177/030006059702500501
25. *Ruepert L., Quartero A.O., de Wit N.J., van der Heijden G.J., Rubin G., Muris J.W.* Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*. 2011;2011(8):CD003460. DOI: 10.1002/14651858.CD003460.pub3
26. *Poynard T., Regimbeau C., Benhamou Y.* Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2001;15(3):355–61. DOI: 10.1046/j.1365-2036.2001.00937.x
27. *Ивашкин В.Т., Полуэктова Е.А., Рейхарт Д.В., Шифрин О.С., Бениашвили А.Г., Ляшенко О.С. и др.* Эффективность наиболее часто назначаемых групп препаратов у пациентов с функциональными расстройствами желудочно-кишечного тракта — синдромом функциональной диспепсии и синдромом раздраженного кишечника (Результаты наблюдательного исследования). *Российский журнал гастроэнтерологии, гепатологии, колопроктологии*. 2016;26(4):14–23. [*Ivashkin V.T., Poluektova Ye.A., Reykhart D.V., Shifrin O.S., Beniashvili A.G.,*

Lyashenko O.S., et al. Efficacy of drugs most commonly prescribed at functional gastrointestinal diseases (functional dyspepsia syndrome and irritable bowel syndrome) observational study results. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2016;26(4):14–23. (In Russ.)]. DOI: 10.22416/1382-4376-2016-4-14-23
28. *Rahman M.Z., Ahmed D.S., Mahmuduzzaman M., Rahman M.A., Chowdhury M.S., Barua R., et al.* Comparative efficacy and safety of trimebutine versus mebeverine in the treatment of irritable bowel syndrome. *Mymensingh Med J*. 2014;23(1):105–13.
29. *Кардашева С.С., Картавенко И.М., Максимова Н.Б., Юрьева Е.Ю., Попова И.Р., Павлов Ч.С. и др.* Эффективность тримебутина малеата в лечении пациентов с функциональной диспепсией: результаты наблюдательного исследования «TREND». *Российский журнал гастроэнтерологии, гепатологии, колопроктологии*. 2018;28(5):67–76. [*Kardasheva S.S., Kartavenko I.M., Maksimova N.B., Yurieva E.Yu., Popova I.R., Pavlov Ch.S., et al.* Efficacy of trimebutine maleate (Trimedat®) in the treatment of patients with functional dyspepsia: Results of the "TREND" observational study. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2018;28(5):67–76. (In Russ.)]. DOI: 10.22416/1382-4376-2018-28-5-67-76
30. *Kountouras J., Gavalas E., Papaefthymiou A., Tsechelidis I., Polyzos S.A., Bor S., et al.* Trimebutine maleate monotherapy for functional dyspepsia: A multicenter, randomized, double-blind placebo controlled prospective trial. *Medicina (Kaunas)*. 2020;56(7):339. DOI: 10.3390/medicina56070339
31. *Yang Y.J., Bang C.S., Baik G.H., Park T.Y., Shin S.P., Suk K.T., et al.* Prokinetics for the treatment of functional dyspepsia: Bayesian network meta-analysis. *BMC Gastroenterol*. 2017;17(1):83. DOI: 10.1186/s12876-017-0639-0
32. *Свистунов А.А., Буторова Л.И., Осадчук М.А., Киреева Н.В., Токмулина Г.М., Ардатская М.Д.* Синдром билиарной боли в свете Римских критериев IV: рациональный подход к выбору спазмолитической терапии в клинической практике. *Доказательная гастроэнтерология*. 2018;7(2):59–69. [*Svistunov A.A., Butorova L.I., Osadchuk M.A., Kireeva N.V., Tokmulina G.M., Ardatskaya M.D.* The biliary pain syndrome in the context of Rome IV criteria: the rational approach to the choice of spasmolytic therapy in the clinical practice. *Russian Journal of Evidence-Based Gastroenterology*. 2018;7(2):59–69. (In Russ.)]. DOI: 10.17116/dokgastro20187259
33. *Ивашкин В.Т., Павлов Ч.С., Попова И.Р., Шульпекова Ю.О.* Тримебутина малеат в лечении функциональных билиарных расстройств: результаты наблюдательного исследования Tribune. *Медицинский Совет*. 2018;21:117–25. [*Ivashkin V.T., Pavlov C.S., Popova I.R., Shulpekova Yu.O.* Trimebutine maleate in the treatment of functional biliary disorders: Tribune study results. *Meditsinskiy sovet = Medical Council*. 2018;21:117–25. (In Russ.)]. DOI: 10.21518/2079-701X-2018-21-117-125
34. *Яковенко Э.П., Агафонова Н.А., Яковенко А.В., Иванов А.Н., Каграманова А.В.* Агонист опиатных рецепторов тримебутин в терапии функциональных расстройств желчного пузыря и сфинктера Одди. *Лечащий Врач*. 2014;2:56–60. [*Yakovenko E.P., Agafonova N.A., Yakovenko A.V., Ivanov A.N., Kagramanova A.V.* Opioid receptors agonist Trimebutine in treatment of functional gallbladder and Oddy's sphincter disorders. *Lechaschi Vrach*. 2014;2:56–60. (In Russ.)].
35. *Vitton V., Delpy R., Gasmi M., Lesavre N., Abou-Berdugo E., Desjeux A., et al.* Is endoscopic sphincterotomy avoidable in patients with sphincter of Oddi dysfunction? *Eur J Gastroenterol Hepatol*. 2008;20(1):15–21. DOI: 10.1097/MEG.0b013e3282eeb4a1
36. *Андреев Д.Н., Маев И.В.* Эффективность тримебутина в рамках лечения функциональных заболеваний желудочно-кишечного тракта и желчных путей: наблюдательное многоцентровое исследование. *Терапевтический архив*. 2021;93(8):897–903. [*Andreev D.N., Maev I.V.* Efficacy of trimebutine in the treatment of functional gastrointestinal disorders: an observational multicenter study. *Terapevticheskii Arkhiv*. 2021;93(8):897–903. (In Russ.)]. DOI: 10.26442/00403660.2021.08.200919
37. *Ogawa N., Nakajima S., Tamada K., Yokoue N., Tachibana H., Okazawa M., et al.* Trimebutine suppresses Toll-like receptor 2/4/7/8/9 signaling pathways in macrophages. *Arch Biochem Biophys*. 2021;711:109029. DOI: 10.1016/j.abb.2021.109029
38. *Корниенко Е.А., Типикина М.Ю., Кубалова С.С., Карпинчук Д.Н., Паролова Н.И.* Новые аспекты механизмов развития и лечения синдрома раздраженного кишечника. *Вопросы практической педиатрии*. 2011;6(5):8–14. [*Kornienko E.A., Tipikina M.Yu., Kubalova S.S., Karpinchuk D.N., Parolova N.I.* New aspects of the mechanisms of development and treatment of irritable bowel syndrome. *Voprosy Prakticheskoi Pediatrii*. 2011;6(5):8–14. (In Russ.)].
39. *Gao M., Zuou H., Zhu Y., Chen Y.* Effect of trimebutine maleate tablets on serum TNF-α, IL-23, ESR, D-D ulcerative colitis in patients with ulcerative colitis. *Chinese Journal of Biochemical Pharmaceutics*. 2017;6:204–6.
40. *Xu J., Hu C., Jiang Q., Pan H., Shen H., Schachner M.* Trimebutine, a small molecule mimetic agonist of adhesion molecule L1, contributes to functional recovery after spinal cord injury in mice. *Dis Model Mech*. 2017;10(9):1117–28. DOI: 10.1242/dmm.029801
41. *Salvioli B.* Trimebutine: A state-of-the-art review. *Minerva Gastroenterol Dietol*. 2019;65(3):229–38. DOI: 10.23736/S1121-421X.19.02567-4
42. *Трухан Д.И., Гришечкина И.А., Быховцев Н.А.* Тримебутин в лечении синдрома раздраженного кишечника и других функциональных гастроинтестинальных расстройств. *Медицинский совет*. 2016;19:82–6. [*Trukhan D.I., Grishechkina I.A., Bykhovtsev N.A.* Trimebutin in the treatment of irritable bowel syndrome and other functional gastrointestinal disorders. *Meditsinskiy sovet = Medical Council*. 2016;19:82–6. (In Russ.)]. DOI: 10.21518/2079-701X-2016-19-82-86
43. *Kountouras J., Chatzopoulos D., Zavos C., Boura P., Venizelos J., Kalis A.* Efficacy of trimebutine therapy in patients with gastroesophageal reflux disease and irritable bowel syndrome. *Hepatogastroenterology*. 2002;49(43):193–7.
44. *Nogi K., Haruma K., Taniguchi H., Yomota E., Okajima M., Hananoki M., et al.* Duodenogastric reflux following cholecystectomy in the dog: Role of antroduodenal motor function. *Aliment Pharmacol Ther*. 2001;15(8):1233–8. DOI: 10.1046/j.1365-2036.2001.01035.x

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