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Inflammation, impaired motor function and visceral hypersensitivity: the main mechanisms of functional disorders of the gastrointestinal tract (materials of the Expert Council and literature review)

Vladimir T. Ivashkin[1], Igor V.Maev[2], Alexander S. Trukhmanov[1], Arkadiy A. Sheptulin[1,*], Tatyana L. Lapina[1], Vladimir I. Simanenkov[3], Kirill A. Sokolov[4]

[1] *Sechenov First Moscow State University (Sechenov University), Moscow, Russian Federation*
[2] *Yevdokimov Moscow State University of Medicine and Dentistry, Moscow, Russian Federation*
[3] *Mechnikov North-Western State Medical University, St. Petersburg, Russian Federation*
[4] *"Bayer" JSC, Moscow, Russian Federation*

Aim. To review the main mechanisms of functional disorders of the gastrointestinal tract and to present the materials of an Expert Council, which was held on 10 December 2021 in Moscow.
Key points. The pathogenesis of the most common functional diseases of the gastrointestinal tract — functional dyspepsia (FD) and irritable bowel syndrome (IBS) is multifactorial and includes motor disorders of various parts of the gastrointestinal tract, visceral hypersensitivity, changes in the intestinal microbiome, impairment of the permeability of the protective barrier, low-grade inflammation of the gastrointestinal mucosa, etc. This often leads to the prescription of a complex of various medications to such patients, which increases the risk of undesirable drug interactions and side effects. Multitargeted therapy involves the use of drugs that simultaneously affect different pathogenetic links. One of these drugs is Iberogast®, which normalizes gastrointestinal motility and visceral sensitivity, has an anti-inflammatory action and is highly effective in treatment of FD and IBS.
Conclusion. In the treatment of functional gastrointestinal diseases characterized by multifactorial pathogenesis, preference should be given to multi-targeted therapy with the use of drugs that have an effect on its various links.
Keywords: gastrointestinal tract, motility, visceral hypersensitivity, inflammation, Iberogast®
Conflict of interest: The Expert Council was held under the technical support of the «Bayer» pharmaceutical company.

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Воспаление, нарушение моторной функции и висцеральная гиперчувствительность: основные механизмы функциональных расстройств желудочно-кишечного тракта (обзор литературы и резолюция Совета Экспертов)

В.Т. Ивашкин[1], И.В. Маев[2], А.С. Трухманов[1], А.А. Шептулин[1,*], Т.Л. Лапина[1], В.И. Симаненков[3], К.А. Соколов[4]

[1] *ФГАОУ ВО «Первый Московский государственный университет им. И. М. Сеченова» (Сеченовский Университет) Министерства здравоохранения Российской Федерации, Москва, Российская Федерация*

[2] *ФГБУ ВО «Московский государственный медико-стоматологический университет им. А.И. Евдокимова» Министерства здравоохранения Российской Федерации, Москва, Российская Федерация*

[3] *ФГБОУ ВО «Северо-Западный государственный медицинский университет имени И.И. Мечникова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Российская Федерация*

[4] *АО «Байер», Москва, Российская Федерация*

Цель публикации. Рассмотреть основные механизмы функциональных расстройств желудочно-кишечного тракта и представить материалы Совета Экспертов, который состоялся 10 декабря 2021 г. в Москве.
Основные положения. Патогенез наиболее частых функциональных заболеваний желудочно-кишечного тракта (ЖКТ) — функциональной диспепсии (ФД) и синдрома раздраженного кишечника (СРК) — является

многофакторным и включает в себя нарушения моторики различных отделов ЖКТ, висцеральную гиперчувствительность, изменения кишечного микробиома, нарушения проницаемости защитного барьера, воспаление слизистой оболочки ЖКТ низкой степени активности и др. Нередко это приводит к назначению таким больным комплекса различных лекарственных препаратов, что повышает риск возникновения нежелательного лекарственного взаимодействия и побочных эффектов. Мультитаргетная терапия предполагает применение препаратов, одновременно влияющих на разные патогенетические звенья. Одним из таких препаратов является Иберогаст®, нормализующий моторику ЖКТ и висцеральную чувствительность, обладающий противовоспалительным действием и оказывающийся высокоэффективным в лечении ФД и СРК.

Выводы. В лечении функциональных заболеваний ЖКТ, характеризующихся многофакторностью патогенеза, следует отдавать предпочтение мультитаргетной терапии с назначением препаратов, влияющих на его разные звенья.

Ключевые слова: желудочно-кишечный тракт, моторика, висцеральная гиперчувствительность, воспаление, Иберогаст®

Конфликт интересов: Экспертный совет состоялся при организационной поддержке фармацевтической компании «Байер».

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On 10 December 2021, the Expert Council was held to discuss the main mechanisms of the occurrence of functional gastrointestinal (GI) disorders under the chairmanship of V.T. Ivashkin, Academician of the Russian Academy of Sciences, I.V. Maev, Academician of the Russian Academy of Sciences, and Professor A.S. Trukhmanov, with the support of the pharmaceutical company Bayer.

Report of V.T. Ivashkin, Academician of the Russian Academy of Sciences, (Moscow) was devoted to the importance of low-grade inflammation, disorders of the stomach and intestinal motility, as well as visceral sensitivity in the pathogenesis of the functional GI disorders. It has been demonstrated that the development of functional gastrointestinal disorders is based on the following mechanisms: dysmotility of the stomach and gut, visceral hypersensitivity, inflammation of the mucous membrane of a low degree of activity and an increase in its permeability, changes in the composition of the microbiota of the gastrointestinal tract, impaired interaction of the brain-intestine axis [1–3]. Pathogenetic mechanisms of functional GI disorders (such as impaired motility and visceral sensitivity) are triggered by existing background factors (genetic predisposition, psychological factors, alimentary errors, food poisoning) [3]. At the same time, inflammatory mediators (histamine, serotonin, interleukins, etc.), changes in the composition of the intestinal microflora, increased gas formation, and increased sensitivity of the receptor apparatus of the stomach and intestinal wall to stretching are involved in the occurrence of GI motility disorders [4]. In turn, disturbances in the stomach and intestinal motility cause the appearance of such complaints as a feeling of heaviness and fullness in the epigastrum after eating, early satiety, pain along the intestines associated with the act of defecation [1, 2]. In addition, a genetically determined violation of cell contacts predispose to inflammation in the GI mucosa. These factors can be aggravated by changes in the intestinal microbiome, which lead to an increase in the production of proinflammatory cytokines, degranulation of mast cells and eosinophils, an increase in the permeability of the protective barrier, followed by the development of inflammation of the gastrointestinal mucosa and the occurrence of clinical symptoms of functional gastrointestinal disorders [5]. A large number of various factors involved in the formation of functional GI disorders make it expedient to use drugs with multitarget action in their treatment, i.e. affecting simultaneously different links in the pathogenesis of functional GI disorders [6].

Professor A.A. Sheptulin (Moscow) dwelled in his report upon the diagnostic algorithm in case of dyspeptic symptoms in patients, as well as on the possibility of prescribing them at the stage of diagnostic search for drugs. It was noted that the diagnosis of functional dyspepsia (FD) only on the basis of compliance of patients' complaints with the Rome IV criteria [7] and the absence of "alarm signs" is fraught with serious errors. The inconsistency of the provisions of the expert conciliation meeting of the European Society of Neurogastroenterology and Motility (ESNM) held in Belgium in 2020 and dedicated to FD was noted. On the one hand, 80 % of the experts participating in the meeting approved the provision according to which esophagogastroduodenoscopy (EGDS) is mandatory for the diagnosis of FD, and, on the other hand, 93 % of the experts admitted the possibility of managing unexamined patients with dyspepsia in the absence of "alarm signs" without endoscopy [8].

The Russian Gastroenterological Association, making clinical recommendations for the diagnosis and treatment of FD, proceeds from the fact that the FD symptoms are not specific and can occur in a variety of diseases, and therefore considers this diagnosis as a "diagnosis of exclusion" [1]. Conditions such as impaired gluten tolerance and lactose intolerance

require to be excluded. For this purpose, the level of tissue transglutaminase is determined and a hydrogen breath test with lactose is performed. Peptic ulcer disease, gastroesophageal reflux disease (GERD), biliary tract disorders, chronic pancreatitis, tumors of the stomach and pancreas, and other diseases can occur under the "mask" of FD. Therefore, patients with suspected FD are required to undergo CBC and biochemistry, stool analysis (including occult blood), ultrasound examination of the abdominal organs, endoscopy (including with a biopsy of the duodenal mucosa to exclude celiac disease), testing for *Helicobacter pylori (H. pylori) infection*, if necessary — other laboratory and instrumental methods of examining [9].

In recent years, the herbal preparation STW5 (Iberogast®) has become widely used in the treatment of FD. In addition to high efficiency, this drug is well tolerated and safe to use [10, 11]. The absence of any influence of the drug on the results of the examination makes it possible to use it already at the stage of diagnostic search.

The resistance of dyspeptic symptoms to ongoing therapy requires the exclusion of the psychogenic nature of existing complaints and requires the consultation of a psychoneurologist with the possible subsequent addition of psychotropic drugs.

The report **of Associate Professor T. L. Lapina** (Moscow) was devoted to the analysis of the causes of dyspepsia after *H. pylori* eradication and modern tactics of its treatment.

Symptoms of dyspepsia (pain and burning sensation in the epigastric region, a feeling of heaviness and fullness in the epigastrium, early satiety) are extremely widespread. In a meta-analysis that included 100 different populations with more than 31,000 individuals examined, the mean prevalence of dyspepsia was 20.8 % (95 % confidence interval (CI = 17.8–23.9 %). Risk factors were female sex (odds ratio (OR) = 1.24 (95 % CI 1.13–1.36), smoking (OR = 1.25 (95 % CI 1.12–1.40), non-steroidal anti-inflammatory drugs (OR = 1.59 (95 % CI 1.27–1.99) and *H. pylori* infection (OR = 1.18 (95 % CI 1.04–1.33) [12]).

Eradication therapy for *H. pylori* infection is considered as a necessary step in the management of patients with symptoms of dyspepsia, including the participants of the ESNM consensus meeting on FD (2020) [8, 13]. Anti-*H. pylori* therapy in *H. pylori*-positive individuals with symptoms of dyspepsia, that is, in fact, in patients with chronic gastritis with dyspepsia, is the therapy of choice, allowing, on the one hand, to identify patients with dyspepsia directly caused by this bacterial infection. On the other hand, recurrence of dyspepsia symptoms after successful eradication of *H. pylori* indicates the presence of a functional disease in patients, namely FD ones [1, 14]. According to the Cochrane meta-analysis, the relative risk of persisting dyspepsia symptoms after anti-H. pilory therapy is 0.90 (95 % CI = 0.86–0.94) [15].

Thus, inflammation of the gastric mucosa, caused by *H. pylori,* does not appear to be the main cause of dyspeptic symptoms. Dyspepsia is based on a range of mechanisms that are in complex interaction with each other. Motor and sensory dysfunction, dysregulation of the gut-brain axis, disruption of the integrity of the mucosa, and changes in the GI microbiota are considered as the basis for the pathogenesis of functional GI disorders, including FD [7, 16].

Impaired gastroduodenal motility and visceral hypersensitivity are classical factors in the pathogenesis of FD [2]. The ESNM consensus meeting on FD identified gastric accommodation disorder, delayed gastric emptying, gastric hypersensitivity to distension, and impaired processing of signals from the gastroduodenal region in the central nervous system as proven pathophysiological mechanisms [13].

For irritable bowel syndrome (IBS), the importance of minimally expressed mucosal inflammation, including intraepithelial lymphocytes and mast cells, has been shown. In FD, the number of intraepithelial lymphocytes in the duodenum is not increased, but changes in their surface markers that determine proliferation and/or differentiation into specialized cells indicate the activation of lymphocytes [17]. Activation of innate immunity in the gastrointestinal mucosa is a rather complex process. Th2 cells attract eosinophils and mast cells to areas of inflammation. Their degranulation leads to the release of pro-inflammatory mediators that can cause epithelial barrier dysfunction and alter the function of nerve endings in the gastrointestinal tract. An increase in the epithelium permeability, in turn, can contribute to the penetration of secondary luminal antigens and further activation of the immune response [17]. The significance of changes in the composition of the GI microbiota in the pathogenesis of functional GI disorders (including FD) is under study [7, 16, 17].

Some common pathogenetic mechanisms and the high frequency of some GI symptoms in the population cause a frequent combination of various functional GI disorders in one patient [2, 7, 16]. Thus, a combination of various clinical variants of FD and IBS was found in 45 % of outpatients, who, based on the compliance of patient complaints with the "Rome III criteria" and the absence of "alarm signs", were diagnosed with a functional gastrointestinal disease [18]. In addition to the frequent intersection of various functional disorders in clinical practice, the combination of FD and gastroesophageal reflux disease (GERD) is widespread. According to a meta-analysis, in the general population, the combination of FD and GERD is 7.41 % (CI = 4.55–11.84 %), the presence of symptoms of FD in patients with GERD occurs in 41.15 % of cases (CI = 29.46–53.93 %), the presence of GERD symptoms in persons with FD — 31.32 % (CI = 19.43–46.29 %) [19].

The involvement of various mechanisms in the pathogenesis of FD and the frequent overlap of FD with other functional disorders and GERD make the strategy of multitarget therapy justified. Iberogast® fully corresponds to that strategy, the diverse effects of which allow to use the drug in both FD and IBS.

The double-blind, placebo-controlled study included 308 patients with FD who received Iberogast® or placebo for 8 weeks. According to the Gastrointestinal Symptom Rating Scale (GSRS) in the STW 5 group, the change in symptoms was 6.9 ± 4.8 points vs 5.9 ± 4.3 points in the placebo group ($p < 0.05$). Treatment tolerance and safety were similar between Iberogast® and placebo [10].

Professor V.I. Simanenkov (St. Petersburg) dwelled in his report on the currently widespread polypragmasy in the treatment of patients, due to the polymorbidity that is often encountered at the present time. Polypragmasy contributes to an increase in the number and severity of side effects, the occurrence of undesirable drug interactions, an increased frequency of hospitalizations and an increase in the risk of death. It has been shown that the simultaneous use of two drugs leads to undesirable drug interactions in 6 % of patients, administration of 5 drugs increases their frequency up to 50 %, and administration of 10 drugs increases the risk of drug interactions to 100 % [20]. Along with the number of drugs taken simultaneously, the duration of therapy is also taken into account in the diagnosis of polypragmasy. The literature more often reports on five to nine drugs used for 90 days or more [21].

There are two types of polypragmasy. "Appropriate polypragmasy" is defined as the prescription of multiple drugs to a patient in a comorbid pathology, while optimizing their interactions and in accordance with the criteria of "Evidence-Based Medicine". "Inappropriate polypragmasy" refers to the prescription of multiple drugs inappropriately or in cases where the intended benefit of their combination is not realized. This option also includes situations where new drugs are additionally prescribed to relieve adverse events associated with polypharmacotherapy [22, 23].

The accent is given to the following main strategies for managing patients with comorbid diseases:

- Sequential therapy involves the active treatment of the disease most relevant at the moment. This implies that the course of comorbid diseases will also improve. Convincing confirmation of this hypothesis in clinical practice has not yet been received.
- The strategy of parallel (simultaneous) polypharmacotherapy reflects the doctor's desire to improve the course of all the patient's diseases and is associated in many cases with undesirable side effects due to drug interactions.
- Deprescribing refers to the planned and controlled process of reducing the dose of drugs that can harm a patient. In particular, the tactics of deprescribing proton pump inhibitors have been studied in details in gastroenterology [24].
- The use of fixed combinations makes it possible to increase the patient's adherence to treatment, however, the number of such combinations used in the treatment of digestive system disorders is still small. Examples are the combination of proton pump inhibitors and prokinetics, and the herbal preparation STW5 (Iberogast®).
- The concept of multi-target (multi-purpose) therapy involves the use of one drug with a wide range of different effects instead of several drugs. Examples of drugs with multitarget activity used in gastroenterology are a non-selective opioid receptor agonist, a stimulator of the synthesis of cytoprotective prostaglandins, and the herbal drug Iberogast® [25]. Multitarget therapy is currently an effective measure against polypharmacy.

K.A. Sokolov, Head of the medical and clinical department of the pharmaceutical company Bayer (Moscow), presented classical ideas and new data on the mechanisms of action and clinical efficacy of the herbal drug STW5 (Iberogast®) in his report, which contains an extract of 9 plants: Iberian bitter (Iberis amara), angelica (Angelica archangelica), chamomile (Matricaria chamomilla), caraway (Carum carvi), spotted milk thistle (Silybum marianum), lemon balm (Melissa officinalis), peppermint (Mentha piperita), May celandine (Chelidonium majus), licorice root (Glycyrrhiza glabra). This drug was developed in Germany and has been used in clinical practice for over 60 years [26]. Iberogast®, as a standardized herbal medicinal product, has been approved based on efficacy and safety data in large randomized clinical trials. However, data on a specific mechanism of action did not exist for a long time, in this connection Bayer conducted a number of additional studies in the last decade, the results of which were presented to the Expert Council.

Experimental and clinical studies have shown that Iberogast® leads to a decrease in the tone of fundus and body of stomach, thus normalizing its accommodation, and an increase in the phase contractile activity of the antrum, providing a prokinetic effect [27, 28]. At the same time, the effect of this drug on gastrointestinal motility is realized through serotonin 5-HT_3 — and 5-HT_4 receptors of sensitive neurons of the submucosal layer and muscarinic M_3 receptors of smooth muscle fibers of the stomach and intestines [29].

Experimental studies revealed that oral administration of Iberogast® reduces the afferent sensitivity of the small intestine to distension, as well as intravenous administration of bradykinin and 5-hydroxytryptophan [30]. It has recently been shown that Iberogast® reduces visceral hypersensitivity by desensitizing the ion channels of the transient receptor potential, which leads to a decrease in the severity of symptoms such as abdominal pain, bloating, nausea, and early satiety [31].

A number of studies of the drug have substantiated the anti-inflammatory effect on the intestinal mucosa. In an experimental study, the drug prevented the development of inflammation of the mucous membrane of the jejunum and ileum in rats, caused by the instillation of 2,4,6-trinitrobenzenesulfonic acid, by reducing the release of tumor-necrotizing factor-alpha and increasing the production of interleukin-10 [32]. The preventive effect of Iberogast® in relation to the development of ulcerative colitis in rats after administration of a 5 % solution of sodium dextran sulfate was comparable to that of sulfasalazine [33]. It has recently been shown that this drug suppresses the production of pro-inflammatory cytokines, reduces their negative impact on the expression of the tight junction protein zonulin (Zo-1), and thereby normalizes the permeability of the GI mucosa [34].

Iberogast® has a gastroprotective effect by suppressing the secretion of hydrochloric acid, increasing the production of prostaglandin E_2 and increasing the secretion of mucus in the stomach [35], and also has anti-*H. pylori* activity [36].

Thus, the multitarget action of Iberogast® determines the expediency of its use in functional diseases of the stomach and intestines.

I.V. Maev, Academician of the Russian Academy of Sciences (Moscow) and **professor A.S. Trukhmanov** (Moscow) noted a wide range of various beneficial effects of Iberogast®, indicating its multitarget action, a high level of evidence of studies on the effectiveness of this drug in the treatment of functional GI disorders, as well as the safety of its use.

Resolution of the Expert Council

"Inflammation, impaired motility function and visceral hypersensitivity: the main mechanisms of functional gastrointestinal disorders" (10 December 2021)

1. Functional GI disorders, such as functional dyspepsia (FD) and irritable bowel syndrome (IBS), are widespread among the population and often combined with each other, as well as gastroesophageal reflux disease, which is due to the commonality of their etiological factors and pathogenetic links.

2. The leading pathogenetic factors of FD and IBS are motility disorders of various parts of the gastrointestinal tract, visceral hypersensitivity, and disruption of the interaction between the gut-brain axis. Further study is required of such possible mechanisms for the development of functional diseases of the stomach and intestines, such as changes in the intestinal microbiome, impaired permeability of the protective epithelial barrier, and inflammation of the gastrointestinal mucosa of a low degree of activity.

3. Clinical symptoms of FD and IBS are nonspecific and can occur in a wide range of organic diseases (peptic ulcer, stomach tumors, etc.), as well as impaired gluten tolerance and lactose intolerance. This necessitates a thorough examination of patients with suspected functional GI disorders with the obligatory conduct of a wide range of laboratory tests, ultrasound examination of the abdominal organs, esophagogastroduodenoscopy (with symptoms of dyspepsia) and colonoscopy (with symptoms characteristic of IBS).

4. If the patient has symptoms of dyspepsia, testing for the presence of *Helicobacter pylori (H. pylori) infection* with subsequent eradication is indicated. Sustained (within 6 months — 1 year) disappearance of dyspepsia symptoms after successful eradication therapy indicates that the patient has *H. pylori*-associated dyspepsia. Preservation of dyspeptic symptoms in a patient after successful eradication indicates their functional nature.

5. The insufficient effectiveness of the treatment of FD and IBS is due to the frequent use of a complex of drugs that affect individual pathogenetic links of these disorders, which often leads to polypragmasy and an increase in the frequency of unwanted drug interactions and side effects. This determines the feasibility of conducting multitarget (multipurpose) therapy based on the use of drugs that simultaneously affect various pathogenetic factors of functional GI disorders. In addition, the resistance of dyspeptic symptoms to ongoing therapy requires the exclusion of the psychogenic nature of existing complaints and requires the consultation of a psychoneurologist with the possible subsequent addition of psychotropic drugs to treatment.

6. The multitarget properties of the herbal drug STW 5 (Iberogast®) (elimination of gastrointestinal motility disorders, as well as visceral hypersensitivity, anti-inflammatory activity, normalization of the permeability of the gastric and intestinal mucosa, gastroprotective effect) determine the high effectiveness of this drug in the treatment of FD and IBS. Wide indications for appointment of the drug (both functional and organic GI disorders) and proven safety predetermine the possibility of its use at the stage of diagnostic search. The presence of an anti-inflammatory effect in combination with other properties makes it reasonable to use Iberogast® in patients with already eradicated *H. pylori infection* and symptoms that persist for a long time.

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Information about the authors

Vladimir T. Ivashkin — Dr. Sci. (Med.), RAS Academician, Prof., Head of the Department of the Propedeutics of Internal Diseases, Head of the V.H. Vasilenko Clinic of the Propedeutis of Internal Diseases, Gastroenterology and Hepatology, I.V. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: ivashkin_v_t@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0002-6815-6015

Igor V. Maev — Dr. Sci. (Med.), RAS Academician. Professor, Head of the Department of Propedeutics of Internal Disease and Gastroenterology, A.E. Yevdokimov Moscow State University of Medicine and Dentistry.
Contact information: igormaev@rambler.ru;
127473, Moscow, Delegatskaya str., 20, build. 1.
ORCID: https://orcid.org/0000-0001-6114-564X

Alexander S. Trukhmanov — Dr. Sci. (Med.), Professor, Department of Internal Disease Propedeutics, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact Information: trukhmanov_a_s@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0003-3362-2968

Arkadiy A. Sheptulin* — Dr. Sci. (Med.), Professor, Department of Internal Disease Propedeutics, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact Information: arkalshep@gmail.com;
119435, Moscow, Pogodinskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0002-1395-9566

Сведения об авторах

Ивашкин Владимир Трофимович — доктор медицинских наук, академик РАН, профессор, заведующий кафедрой пропедевтики внутренних болезней; директор клиники пропедевтики внутренних болезней, гастроэнтерологии и гепатологии им. В.Х. Василенко и ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет)
Контактная информация: ivashkin_v_t@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-6815-6015

Маев Игорь Вениаминович — доктор медицинских наук, академик РАН, профессор, заведующий кафедрой пропедевтики внутренних болезней и гастроэнтерологии ФГБОУ ВО «Московский государственный медико-стоматологический университет им. А.И. Евдокимова.
Контактная информация: igormaev@rambler.ru;
127473, г. Москва, ул. Делегатская, д. 20, стр. 1.
ORCID: https://orcid.org/0000-0001-6114-564X

Трухманов Александр Сергеевич — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет).
Контактная информация: trukhmanov_a_s@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0003-3362-2968

Шептулин Аркадий Александрович* — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет).
Контактная информация: arkalshep@gmail.com;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-1395-9566

Tatyana L. Lapina — Cand. Sci. (Med.), Assoc. Prof. Chair of Internal Diseases Propedeutics, Gastroenterology and Hepatology, Sklifosovsky Institute of Clinical Medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact Information: lapina_t_l@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/ 0000-0003-4456-8725

Vladimir I. Simanenkov — Dr. Sci. (Med.), Prof., Departament of Internal Diseases, Clinical Pharmacology and Nephrology, I.I. Mechnikov North-West State Medical University.
Contact information: visimanenkov@mail.ru;
191015, St.-Petersburg, Kirochnaya str., 41.
ORCID: https://orcid.org/0000-0002-1956-0070

Kirill A. Sokolov — obstetrician-gynecologist, manager of medical organizations, Head of the Medical and Clinical Department in Russia, Ukraine and the CIS countries, Bayer Consumer Health.
Contact information: kirill.sokolov@bayer.com;
107113, Moscow, 3rd Rybinskaya str., 18, build. 2.
ORCID: https://orcid.org/0000-0002-8358-3963

Лапина Татьяна Львовна — кандидат медицинских наук, доцент кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет).
Контактная информация: lapina_t_l@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0003-4456-8725

Симаненков Владимир Ильич — доктор медицинских наук, профессор кафедры внутренних болезней, клинической фармакологии и нефрологии ФБГОУ ВО «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Министерства здравоохранения Российской Федерации
Контактная информация: visimanenkov@mail.ru;
191015, г. Санкт-Петербург, ул. Кирочная, д. 41.
ORCID: https://orcid.org/0000-0002-1956-0070

Соколов Кирилл Александрович — врач — акушер-гинеколог, менеджер медицинских организаций, руководитель Медицинского и клинического отдела России, Украины и стран СНГ, «Байер Консьюмер Хэлс».
Контактная информация: kirill.sokolov@bayer.com;
107113, Москва, 3-я Рыбинская ул., д. 18, корп. 2.
ORCID: https://orcid.org/0000-0002-8358-3963

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* Corresponding author / Автор, ответственный за переписку