IRRITABLE BOWEL SYNDROME — A DISEASE WITH MANY UNKNOWN VARIABLES (SOME THERAPEUTIC ASPECTS)

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Key words: irritable bowel syndrome, functional diseases, serotonin receptors, antidepressants, antipsychotics, antispasmodics, probiotics

Irritable bowel syndrome (IBS) is a functional disease, the etiology of which is unknown to the end, and its treatment has more questions than answers. IBS integrates clinical conditions such as pain and/or discomfort in the abdomen, which are facilitated after defecation and associated with a change in frequency of bowel movements and/or form of feces [36]. IBS was even defined as a syndrome of "Gulf War", when many soldiers who participated in the Gulf War in 1991, suffered from the disease [8].

The prevalence of IBS in most countries is on average 20%, ranging from 9 to 48% in different populations. Social and cultural level of the population largely determines the appeals of the population about the disease. Studies in the US have shown that IBS leads to significant financial losses for employers. The prevalence of IBS in Turkey — 7,4-19,1% and is more common in women — from 64% to 69% [29, 62]. Similar rates have been reported in the United States and Europe in the range of 6.2% to 25% [60, 80]. Many patients with IBS do not seek help in a timely manner, and when they do, the diagnosis may be already a difficult task. Presence of IBS is the disease which occurs in the population from 5% to 20%, which is described in several reports [45, 48, 55]. Prevalence of the disease varies depending on the diagnostic test used to determine IBS — from Manning criteria that do not define minimal time duration of the symptoms and lead to a higher prevalence than Rome criteria [10]. In general, the prevalence is increasing in young people, women and those patients who have other functional disorders of the gastrointestinal tract [103].

In Russia not more than 10% of patients with IBS appeal for medical help, so information about the frequency and prevalence of the disease can’t be considered reliable. According to a survey of 2016 workers and employees of Moscow, IBS was diagnosed in 25.8%. Moreover, in Russia, unlike some other countries, IBS is not a "favorite" diagnosis among doctors, and it has only recently become more popular. The vast majority — 55% of patients — for the first time turn to the district physicians, accounting for 12% of all patients. 25% of patients first come to a gastroenterologist, accounting for 28% of patients examined by a gastroenterologist. IBS accounts for 28-70% of all requests for medical aid in a structure of the gastroenterological diseases. 50% of the time of a doctor-gastroenterologist is spent on the treatment of patients with IBS. Approximately 15% of patients are initially treated by a psychiatrist about certain psychopathology accompanying for IBS. 5% of patients come to doctors of other specialties — often to gynecologists, surgeons, endocrinologists [1]. Predictors for seeking medical help for IBS include severe symptoms (such as pain) and psychological problems (e.g., anxiety, depression, violence, behavior illnesses, somatic attribution). IBS positive characteristic is that it is not at increased risk of developing more serious diseases, such as ulcerative colitis and colon cancer. On the other hand, it is a disorder that annoys (at best) or becomes debilitating and disturbing (at worst), and can be difficult to diagnose and treat, dramatically reducing the quality of life of patients [64].

IBS triggers:

- common events, such as eating and distention with gas formation in the colon can cause excessive reaction in a person with IBS;
- some medicines and food can cause spasms in some people. Sometimes spasm slows transit of intestinal contains, which leads to constipation;
- chocolate, dairy products or large amounts of alcohol are often the "culprits" of development or can provoke an aggravation IBS;
- caffeine can cause watery stool in many people, but most often causes diarrhea in patients with IBS;

– women with IBS may have more symptoms during menstruation, as hormonal stress may strengthen IBS symptoms.

IBS is a chronic relapsing, remitting and functional disorder of the gastrointestinal tract. In the past, IBS was considered as a diagnosis of exclusion. But today, according to some researchers, it is no longer detected by process of exclusion, but determined by using a certain differential range [59].

IBS is determined by clinical criteria which include the presence of abdominal pain or discomfort and changes in the intestinal status in the absence of "red flags" or anxiety symptoms, such as weight loss, anemia and a number of other symptoms. The first of these, Manning criteria, were described over 30 years ago [100]. Subsequently criteria for IBS were developed in Rome as a result of a consensus of expert opinions — in 1990 (Rome I), which were revised at the two subsequent consensus and simplified with updates in 1999 and 2006. [19, 20, 21, 35, 36]. The main symptoms of these criteria show only a small fraction of real signs for the diagnosis of IBS [106]. However, there are no accurate biomarkers for the complete diagnosis of IBS [104]. IBS-Jennifer website is of interest ***(http://www.ibsjennifer.com)*** — Internet system for scoring (points), which uses all the criteria: Kruis, Manning and Rome (I-III). Patients on their own or with the help of a specialist may identify these criteria, taking into account the type of feces. As a result, a number of international organizations and researchers recommend the use of this diagnostics when making a positive diagnosis of IBS without the need of in-depth studies [30, 41].

IBS is often combined with other functional disorders, such as fibromyalgia, chronic fatigue syndrome (50% of cases), the pathology of the temporomandibular joint (in 64% of cases), chronic pelvic pain (in 51% of cases), with a number of other chronic pain syndromes [94].

Causes of IBS are still unclear, and it is unlikely that a single pathogenesis determines the various manifestations of this heterogeneous disease. There is an evidence that inflammatory bowel diseases may cause symptoms of IBS. Patients with inflammatory bowel diseases, particularly ulcerative colitis in remission, had expressed symptoms similar with IBS [96]. This picture can be observed due to the

ongoing subclinical minimal inflammation [58]. Current postinflammatory motility disorders have also been demonstrated in inflammatory bowel disease patients in the study by V. Loening-Baucke et al. [84]. Development of IBS-type symptoms after acute bacterial or viral gastroenteritis is studied well [97]. This variant — postinfectious IBS — is stipulated by the constant minimal chronic inflammation of the intestinal mucosa [1], or perhaps postinfectious violation of absorption of bile acids [79].

A number of other researchers propose to consider the violation of microbial landscape of the intestine as etiological factor in the pathogenesis of IBS. These disorders include both changes in the colon pool of commensal bacteria [33], and the presence of bacterial overgrowth in the small intestine, determined by the hydrogen breath test in the subgroup of patients with IBS. Symptoms, such as bloating, discomfort and diarrhea, are common for both syndromes — bacterial overgrowth syndrome and IBS are often combined [92, 93]. On the basis of these etiological assumptions a certain niche in the treatment of IBS is taken by antibiotics and probiotics-enteroseptics.

A role in the formation of IBS can play genetic factors. Almost three times more common symptoms similar to IBS are in families of patients with IBS than in relatives who do not suffer from this disease [32]. Is this a genetic predisposition or acquired forms of family behavior has not been studied today. Twin studies show that there is a high consistency of IBS in monozygotic unlike heterozygous twins [56, 57]. However, IBS in parents was more powerful predictor of disease than the presence of monozygotic twins with IBS [57]. Despite these observations, the results of genetic studies of IBS are very contradictory [7, 31].

Recent studies have been identified cascade of pathophysiological disorders between gastrointestinal tract and related peripheral and central mechanisms of pain perception. However, it is possible that these are the secondary complications rather than predictors of IBS. They include disorders of the immune regulation [3], increased permeability of the intestinal wall [52], changes in serotonergic

transmission in the gastrointestinal tube [4], gastrointestinal dysmotility [73] and visceral hypersensitivity [44].

IBS is a consequence of stress disorder with impaired brain-gut connection, the gastro-intestinal homeostasis and, based on recent data, a low degree of inflammation and microflora changes. The immune system is an important regulator of the brain-gut axis. Toll-like receptors (TLRs) are cells recognizing foreign molecules and regulating innate immunity. In patients with IBS activation of TLR8 in response to increased levels of cytokines IL1β, IL6, IL8 and TNF was revealed. In addition, patients with IBS also had TLR2 high activity in response to increased TNF, TLR3-induction with increasing levels of IL-8, TLR4-induction with increasing levels of TNF and IL1β, TLR5-induction with increasing levels of IL1β and TNF and TLR7-induction upon the increasing level of IL-8. No differences in the activity of TLR1, TLR6 and TLR9 were found. Furthermore, IBS patients had significantly elevated plasma levels of cortisol, IL-6 and IL-8. These data clearly demonstrate increased levels of cytokines and reactive high activity of periphery TLRs in patients with IBS, thus indicating some immune dysregulation in IBS patients [5].

Psychiatric comorbidity is common in patients with IBS: about 70% to 90% of people, who appeal for medical help to gastroenterologists with IBS, have symptoms of a mental disorder. This can be a panic disorder, generalized anxiety disorder, social phobia, post-traumatic stress disorder, and major depressive disorder. Conversely, people with IBS symptoms, who do not appeal for medical care, estimated from 50% to 86% of the population, as a rule, do not have psychiatric symptoms [68, 81].

Although the etiology of IBS is still unclear, there is an evidence of a pathophysiological link between the central nervous system and the "enteric nervous system" (ENS) [70]. Stress is known to aggravate intestinal symptoms in IBS patients and healthy subjects, and gastrointestinal symptoms such as nausea, abdominal pain, weight loss/gain is frequently observed in patients with mood and anxiety disorders, pointing to a common etiology in mental health and some of the functional gastrointestinal disorders [9, 25, 67]. IBS occurs in 27% of patients with depression

[69], 59% of patients with dysthymia, 58% of patients with bipolar depression [54]. G. D. Tollefson et al. [15] reported that 37% of patients with generalized anxiety disorder met criteria for IBS. A number of studies have reported a correlation between IBS and panic disorder [11, 61, 85]. Furthermore, S. Gupta et al. identified IBS in 19% of patients with schizophrenia [87], and P. S. Masand et al. revealed that IBS was common among patients seeking treatment for alcohol dependence [53]. Frequent associated mental illness and the lack of identification of organic causes of IBS increase the likelihood that the basis of mood disorders or anxiety may be causally associated with IBS, and that antidepressants and anxiolytics can alleviate the symptoms of this disease.

The main classes of receptors involved in the regulation of motor-evacuation function of the gastrointestinal tract, are cholinergic, adrenergic, dopaminergic, serotonergic, motilin and cholecystokinin ones. Drugs that are used for depressive and anxiety disorders, panic attacks and other autonomic dysfunction, act on the same receptors that are responsible for motor-evacuation function of the gastrointestinal tube. Let’s consider main receptors the effect on which produces antidepressant and anxiolytic effects in parallel with normalization of gastrointestinal motility in patients with IBS.

Serotonin has well-studied effects on intestinal motility, secretion and sensitivity through the central and peripheral neuro-mediator ways, making it a key pharmaceutical remedt in the treatment of IBS [16]. Over 80% of serotonin in the human body is concentrated in the enterochromaffin cells of the gastrointestinal tract [38]. Serotonin is released from these cells in response to chemical or mechanical irritation of the mucous membranes [37], or in response to stress in experimental models [77]. ENS consists of semi-autonomic effector systems associated with the central autonomic system. With the release of serotonin from the enterochromaffin cells, initiation of vagal reflexes happens — peristaltic, excretory, vasodilators, nociceptive. Parasympathetic and sympathetic nervous systems form ENS through afferent and efferent connections. Current bidirectional relationship "brain-gut axis" with the participation of 5-HT have a significant impact on the effector

systems. Broken 5-HT-transmission can cause both intestinal and extraintestinal symptoms of IBS [16].

Serotonin receptors, particularly the 5-HT_3 and 5-$HT_{4,}$ are involved in sensory and reflex responses to stimuli upon gastrointestinal disorders, causing manifestations such as vomiting, constipation or diarrhea, eating disorders, abdominal pain, altered sensorimotor reflexes [83]. It has been suggested that selective serotonin reuptake inhibitors (SSRIs) may affect the function of 5-HT_3 receptors and improve the symptoms of IBS and related depression in patients. Tricyclic antidepressants (TCAs — amitriptillin, imipramine), a number of SSRIs antidepressants, such as fluoxetine, paroxetine, citalopram, klopiramin, litoksetin, trazodone and some SNRIs (duloxetine), improve IBS symptoms in a number of studies and reviews [27, 34, 51]. Long-term side effects are common with antidepressants and related to the anticholinergic, serotonergic, sedatives, antihistamines, alpha-adrenergic effects. These effects must be taken into account when choosing the approach to treatment, as described above antidepressants affect intestinal motility of patient, function should also be considered when choosing the antidepressants [90] (Fig. 1).

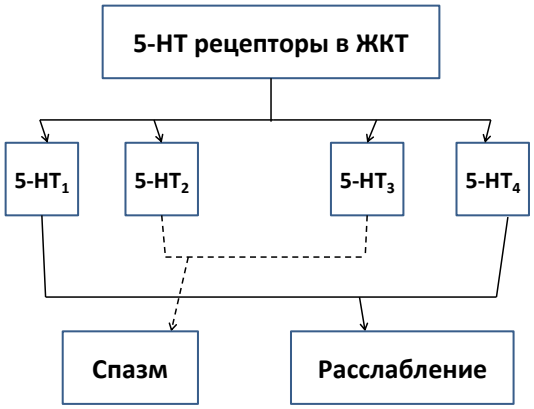

Fig. 1. Main roles of 5-HT-receptors in the gastrointestinal tract.

TCAs, as studied in several studies, improve IBS symptoms (pain and diarrhea) due to strong anticholinergic and sympathomimetic effects, have a good hypnotic effect, indicated for patients with concomitant extraintestinal pathology

[17, 34, 91]. A recent double-blind, placebo-controlled trial with SSRI citalopram has shown a good efficacy in a number of IBS symptoms as compared with placebo in patients with depression [49, 82]. Other studies using SSRIs (paroxetine, fluoxetine) for IBS have shown the advantage of improving psychological symptoms in patients with gastrointestinal symptoms [24, 78]. A notable side effect of SSRIs is diarrhea, i.e. they may be useful for patients with constipation-predominant IBS (IBS-C) [40].

Thus, the theoretical justification for the use of centrally acting drugs, such as antidepressants, in the treatment of IBS are rather strong and include anxiolytic effects of these drugs on central mechanisms, have a positive effect on the symptoms of IBS (waking, symptoms of anxiety, increased stress-response), have antihyperalgic effects and improve the mood of patients. Use of low-dose TCAs and full-dose SSRIs in selected patients (or groups) is promising, although individual dosage and patient awareness are needed to avoid side effects and provide treatment. Reasons for the inefficiency of antidepressants in subgroups of patients may be related to differences in the pathophysiology and with possible differences in genetic IBS polymorphisms in each patient. Regular use of benzodiazepine anxiolytics is not recommended because of the risk of forming addiction [71].

As mentioned earlier, 5-HT_1, 5-HT_3 and 5-HT_4 receptor subtypes play an important role in motor, sensory and secretory functions of the gastrointestinal tract [37]. Drugs that directly affect 5-HT-receptors, in contrast to SSRIs and TSAs, modulate 5-hydroxytryptamine by binding to 5-HT-receptors. Intestinal functions of 5-HT-receptors are associated with smooth muscle, increased number of bowel movements, and with a reduction of the intestinal transit time [88, 101]. Blockade of 5-HT_3 receptors, in particular by the antiemetic agents type of ondansetron, leads to constipation [43]. During the last decade blockers of 5-HT_3 receptors have been developed and tested — alosetron and silansetron in diarrhea-predominant IBS (IBS-D). In a recent systematic review and meta-analysis, 11 randomized controlled studies were identified comparing these two 5-HT_3 antagonists with placebo [26]. Nevertheless, some rare adverse effects, including severe ischemic colitis, constipation, led to the fact that alosetron production and silansetron studies were

suspended [39]. Alosetron is now available only on strict conditions in the United States for patients with severe refractory IBS-D, who failed to respond to first or second-line therapy.

Antidiarrheal drug loperamide, which is used by many patients with IBS-C, relieves symptoms of the disease by reducing the frequency and improving stool consistency. Loperamide acts on opioid receptors in the myenteric-plexus, resulting in slowing colonic transit and improving stool. In two randomized controlled studies [6, 66] loperamide was not more effective than placebo for pain in the abdomen or main IBS symptoms, but it was effective in improving the consistency and stool frequency in patients with diarrhea [28]. Another study showed that loperamide improved consistency and stool frequency and/or intensity of pain in approximately one third of patients [41]. A number of guidelines for the treatment of IBS recommend the use of loperamide for diarrhea, but not with abdominal pain, as well as propose the course use of loperamide or to relieve symptoms without the risk of tachyphylaxis after chronic consumption as needed [102].

Agonists of 5-HT_4 receptors have been proposed for the treatment of IBS-C concerning their prokinetic effects. One of these drugs is tegaserod — partial agonist of 5-HT_4 receptors. A systematic review and meta-analysis showed that tegaserod was superior to placebo in IBS-C. Most studies relating to tegaserod conducted with women, and as a result, the drug was originally approved for the treatment of IBS-C only in women. However, the marketing of tegaserod was also suspended, when they began to communicate information about a possible increase in cardiovascular and cerebrovascular events in patients taking the drug [13].

Another drug aimed at combating constipation in IBS is quite well studied — lubiproston — prostaglandin derivative, a selective chloride channel activator that facilitates back diffusion of chlorides, sodium and water into the intestinal lumen. Lubiproston is approved by the FDA for the treatment of chronic idiopathic constipation in both men and women at a dose of 24 mg 2 times a day, and in women with IBS-C — 8 mg 2 times a day. In phase 2 clinical trials used daily lubiproston doses of 16 mg to 48 mcg in IBS-C, which significantly improved the symptoms of

IBS. However, side effects were also increased at higher doses [14]. In the third test phase the use of lubiproston at 8 mg 2 times a day up to 12 weeks showed significant benefit compared with placebo in patients with IBS-C (mainly female) [6]. Studies have shown significant improvements in abdominal discomfort and/or pain, bloating, stool consistency and constipation. Reported lubiproston side effects include nausea, diarrhea and abdominal pain, it is contraindicated in intestinal obstruction and pregnancy [46].

Drugs that selectively inhibit D_2-receptors (dopamine) are of great interest in the treatment of motor-evacuation gastrointestinal and psychosomatic disorders are. One of them is the founder of the group benzamides — sulpiride, synthesized in 1966. Sulpiride selectively blocks postsynaptic D_2-receptors, resulting in slowing down neuronal D_2 transmission (antidopaminenergy activity) [76], without affecting D_1-, D_4-dopamine receptors (limbic system), α-adrenergic and M-cholinergic receptors, H_1-histamine and 5-HT-receptors, unlike conventional antipsychotic drugs. Antipsychotic effect of therapeutic doses of sulpiride is combined with a low probability of extrapyramidal symptoms [99], observed only in patients receiving very high doses of sulpiride — 2 times more than the average therapeutic dose. It should be said that if clinically effective daily dose ranges from 100 to 1800 mg, considered complication of neuroleptic therapy is associated with dose exceeding 2000 mg/day, in small amounts (100-300 mg/day) sulpiride has prodopaminenergy activity [18]. Prodopaminenergy sulpiride activity contributes to its activating (antiasthenic), antidepressant (thymoleptic) action and can contribute to the improvement of cognitive functions. Sulpiride has a favourable somatotropic action associated with both central (suppression of dopamine receptors in the vomiting trigger center of the brain) and peripheral (normalization of gastric, small intestine and colon, gall bladder motility) influence of neuroleptics. It is shown in particular that the drug has antiemetic and antidyspepsic properties [65, 107]. Somatotropic effects of sulpiride are used in cardiology, pulmonology, neurology and especially widely in gastroenterology. Thus, the comparative open study involving 60 patients with IBS has shown the superiority of sulpiride in comparison with traditional (basic)

IBS therapy [2]. It is found in particular that the proportion of patients with complete/marked syndrome reduction in patients taking antipsychotic reaches 85%. The same indicator in patients with basic therapy is only 10%. Moreover, sulpiride effectively affects manifestations of IBS (abdomenalgy, stool changes), and the accompanying somatisation manifestations of anxiety and depression. Sulpiride is widely studied in trials, showing combined positive effects upon IBS with anxiety-depressive and others dysthymic disorder [50, 89, 95]. In our practice, during the treatment of patients with IBS, we prescribe sulpiride (prosulpin, produced in Prague, PRO.MED.TSS) 50 mg 2-3 times a day as the main psychoactive drug up to 3 months or 6-10 days at the beginning of the course of receiving SSRIs for the relief of symptoms of serotonin syndrome (nausea, dizziness, anorexia, weakness, drowsiness), which often occurs at the beginning of treatment before the achievement of the level of saturation or "plateau", i.e. the output to a therapeutic level.

The main symptom of IBS is a pain caused by spasm, which is based on an involuntary contraction of the smooth muscle of the intestine not accompanied by their immediate relaxation. UK National Institute for Health and Clinical Excellence issued new guidelines for the diagnosis and treatment of IBS in primary care. Based on a thorough analysis of clinical data, it was concluded that the drugs of first choice for the treatment of patients with IBS should be considered as antispasmodics — drugs that eliminate spasm of smooth muscles of internal organs [75]. Practical Global Guideline IBS of the World Gastroenterology Organization WGO 2009 name a group of antispasmodics as the primary therapy of pain syndrome, pointing out that "the availability of drugs varies greatly in different regions of the world", thus giving some freedom of choice of spasmolytic in each state. In the national IBS guidelines the main antispasmodics of different groups are recommended: otilonium, trimebutine, cimetropium, hyoscine, pinaverium, alverine, mebeverine, and peppermint oil. They all showed significant benefit compared with placebo [75]. In clinical practice, antispasmodics are prescribed for the relief of postprandial symptoms 30 minutes before a meal. In Russia upon IBS preference is given to

highly selective advantage myotropic antispasmodics, such as mebeverine and pinaverium.

Mebeverine (Duspatalin, Abbott Products Ltd.) is an antispasmodic, which has been successfully used in the treatment of IBS for many years. It causes antispasmodic action, normalizing bowel motor function [22]. At therapeutic doses of mebeverine has a direct blocking effect on the sodium channels, which restricts the inflow of Na+ and prevents the sequence of events leading to muscle spasm. Besides muscarinic receptors, smooth muscle cells in the wall of the gastrointestinal tract also have a1-adrenoceptors associated with Ca2+ depot. This depot, located on the cell membrane, constantly restores the level of Ca2+ from the extracellular space. Norepinephrine receptor stimulation leads to the mobilization of Ca2+ from depots in intracellular space — a process stipulating the opening of K+ channels, which leads to a hyperpolarization and lower tone. Mebeverine blocks filling depot by extracellular Ca2+. Thus, if a1-adrenoceptor is activated in the presence of the drug, depot is emptied and can't be filled up again. Accordingly, the outflow of K+ is short-term, and there is no permanent relaxation or hypotension. While receiving an oral dose of 135-270 mg 3 times a day, it does not cause the typical anticholinergic side effects, such as dry mouth, blurred vision and impaired urination. The frequency of side effects caused by Mebeverine was not higher than placebo. This drug is now sold in about 56 countries, and its efficacy and tolerability have been demonstrated in 10 controlled and many open clinical studies [74, 98]. Upon IBS Duspatalin is prescribed at 1 capsule (200 mg) 2 times a day, taken 20 minutes before a meal.

Dicetel® (Abbott Products Ltd.), the main active ingredient of which is a pinaverium bromide, is an antispasmodic with myotropic action — a calcium antagonist for the treatment of intestinal motility [105]. It selectively blocks the potential-sensitive calcium channels of smooth muscles of the intestine and prevents excessive flow of calcium into the cell. In contrast to other calcium antagonists, Dicetel® shows equal affinity to the channels in the available and inactivated state, which causes its high efficiency and lack of habituation [72]. Balanced work of gastrointestinal smooth muscle apparatus depends on the concentration of calcium in

the cytoplasm of the myocyte and its movements through the cell membrane. Calcium ions play a role not only in conjunction "excitation-contraction", but also in conjunction "excitation-relaxation". L-type calcium channels of gastrointestinal smooth muscle cells are activated by 2 ways:

- the first, the most thoroughly studied, characterized by depolarization of the cell membrane by the action of a nerve impulse, followed by contraction of the smooth muscle cells;
- the second way comprises the calcium channel activation by digestive hormones and mediators, such as cholecystokinin, gastrin or P-substance. By binding to specific receptors, they activate the receptor-operated Ca2+ channels, causing a depolarization of the cell membrane and leading to the opening of potential-dependent calcium channels. If calcium channels are blocked by pinaverium bromide molecules, the action of the aforementioned digestive hormones and mediators can’t be realized.

Thus, pinaverium bromide inhibits not only bowel hypermotor function, but the path involved in visceral hypersensitivity — the second IBS indication. Furthermore, in the membranes of human intestinal smooth muscle cells calcium channels have recently been discovered, which are sensitive to mechanical stress. Apparently, they are a zone of interaction between smooth muscle cells and interstitial cells of Cajal, pacemaker cells of the intestine. The existence of this type of calcium channels may change the perception of gastrointestinal smooth muscle from "purely motor organ" to organ having both motor and sensory function.

The efficacy of Dicetel® in patients with IBS of all types is shown in a large number of studies, both in our country and abroad [12, 23, 42, 74, 86]. Most researchers show good and very good results in complete relief of pain and IBS reduction in patients receiving Dicetel® as monotherapy in the standard dose (at 60%). Moreover, in some patients with IBS-C (mainly patients with mild to moderately severe pain), receiving Dicetel®, except pain relief, there is an independent stool. Decrease in intestinal transit time is mainly found due to the acceleration of its speed in the distal parts of the intestine. Dicetel® acts mainly at the

level of the colon and has indirect effects associated with a decrease in intraluminal pressure, which facilitates the passage of bile, and indirectly affects motility by stimulating it upon the constipations of functional character, including IBS-C.

Dicetel® in the acute period (3-6 days) is prescribed at 100 mg 2-3 times a day during meals. After calming down the aggravation, maintenance dose of pinaverium bromide is a standard dose — 50 mg 3-4 times a day prescribed for the course from 2 to 6 weeks or more. Acting selectively on the intestine, Dicetel® has no side anticholinergic effects, so it can be safely used in patients with glaucoma and prostatic hypertrophy.

Other methods of IBS treatments, including psychological ones (World Gastroenterology Organization, 2009)

Common non-pharmacological recommendations:

- discussion of his anxieties with the patient helps decrease complaints and is aimed at the reduction of unnecessary agitation;
- reduction of unwillingness to receive treatment. Patients may avoid activities that, in their opinion, cause the appearance of symptoms, but "protest" against the treatment adversely affects the prognosis;
- cancerophobia discussion;
- discussion and an attempt to resolve stress factors;
- regular food intake, consumption of adequate amounts of fluid and appropriate physical activity can bring overall beneficial effect, but there is no evidence upon IBS.

In addition to general approaches described above, it is necessary to establish a trusting relationship of doctor and patient with IBS, more formal psychological intervention can be applied in certain circumstances, depending on its availability in the appropriate situation and upon doctor experience. Such approaches may include: cognitive/behavioral therapy, both group and individual; behavioral techniques aimed at modifying dysfunctional behavioral responses.

Hypnotherapy (the use of the therapeutic properties of conventional hypnotherapy to control the functions of the intestine to help relieve symptoms) has

been studied for the treatment of IBS and aims to reassure the patient to focus its attention on improving the intestinal symptoms. In Cochrane review published in 2007, four studies demonstrated high efficacy of hypnotherapy to reduce abdominal pain and other symptoms of IBS compared with conventional medical treatment [47]. Thus, psychological or behavioral therapies may be effective in treating IBS and may be used alone or in combination with pharmacologic therapy. Intern has a number of problems for the implementation of behavioral or psychological therapy — motivation of the patient, his/hers interest in the treatment, the absence of an experienced psychotherapist or clinical psychologist (ideally — with a good knowledge of IBS gastroenterological aspects) and the high cost of such a treatment.

Upon IBS a variety of additional treatments are also used: physiotherapy, physiotherapy, methods based on the principle of biofeedback.

Criteria for the effectiveness of therapy of IBS:

- cessation of symptoms or decrease in their intensity;
- relief of pain and dyspeptic syndromes, normalization of stool and laboratory parameters (remission);
- improvement of health with no significant positive dynamics of objective data (partial remission).

IBS is a common chronic and recurrent disease that significantly affects the quality of life of patients and is associated with a big health and economic burden. Although reliable biomarkers for the diagnosis of IBS are still not found, the definition of the symptoms on the basis of standardized diagnostic criteria allowed to bring together the pathophysiological principles of treatment of patients in more homogeneous groups and move away from IBS as a diagnosis of exclusion.

Various treatment options are available now for patients with IBS, although most of them are not effective in all the patients, even within a specific subtype. Given the complex and multifactorial nature of IBS, the optimal treatment should be individually and patient-centered. Currently, we investigate a number of drugs with new mechanisms of action in IBS. Future studies of the pathophysiology

of IBS will make new and effective diagnostic and therapeutic strategies more affordable (Fig. 2) [63].

Drug class	Name	Mechanism of action
IBS-C		
Ileal bile acid transporter inhibitor	IBAT inhibitor A3309[137]	Partially blocks the reabsorption of bile acids in the ileum leading to an increase in bile acids in the colon, which results in increased secretion and colonic motility
Guanylate cyclase C agonist	Linaclotide	Increases chloride and bicarbonate secretion into intestinal lumen
Opioid antagonist	Naloxone, naltrexone	Decreases intestinal fluid absorption and decreases inhibition of peristalsis and secretion
5-HT_4 agonist	Prucalopride	Increases intestinal motility
Bile acid	Sodium chenodeoxycholate[138]	Induces electrolyte secretion and accelerates colonic transit
IBS-D or nonconstipating IBS		
κ-Opioid receptor agonist	Asimadoline	Activates opioid receptors, which may reduce visceral perception
Carbon-based adsorbent	AST-120[139]	Adsorbs luminal substances including serotonin and bile acids
CRF antagonists	Pexacerfont, GW876008	Blocks CRF_1 receptors to potentially decrease gastrointestinal motility and visceral sensitivity
Proanthocyadin	Crofelemer	Reduces chloride ion secretion via CFTR channel
2,3-Benzodiazepine modulator	Dextofisopam	Modulates autonomic responses
SNRI	DDP-225	May increase synaptic levels of norepinephrine to reduce visceral pain; inhibits intrinsic cholinergic neurons
Serotonin synthesis inhibitor	LX1031[140]	Reduces gastrointestinal levels of serotonin
5-HT_3 antagonist	Ramosetron	Blocks 5-HT_3 receptors to slows gastrointestinal transit and decreases visceral sensitivity
Pain and/or discomfort		
SSRIs and SNRIs	Antidepressants	Blocks reuptake of serotonin (SSRI, SNRI) and norepinephrine (SNRI)
Glucagon-like peptide-1 analogue	ROSE-010[141]	Inhibits small intestinal motility

Abbreviations: 5-HT, serotonin; CFTR, cystic fibrosis transmembrane conductance regulator channel; CRF, corticotropin-releasing factor; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

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Fig. 2. "Future" in the treatment of IBS.

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Irritable bowel syndrome — a disease with many unknown variables (some therapeutic aspects)

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Key words: irritable bowel syndrome, functional diseases, serotonin receptors, antidepressants, antipsychotics, antispasmodics, probiotics

The present review focuses on irritable bowel syndrome, presenting the epidemiology, pathophysiology, clinical course and treatment of this disease. It also discusses the historical issues of forming stages of understanding of the digestive system functional disorders, which responded to the view of problem in each period of the medicine development. Special attention is paid to the psychosomatic component of irritable bowel syndrome. Different etiological variants of the disease and the basic schemes of its treatment are described.