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REVIEW

PATHOPHYSIOLOGICAL CONCEPTS OF FUNCTIONAL DYSPEPSIA AND IRRITABLE BOWEL SYNDROME FUTURE PHARMACOTHERAPY

ŁUKASZ DOBREK* and PIOTR J. THOR

Department of Pathophysiology, Medical College, Jagiellonian University,
18 Czyst St., 31-121 Kraków, Poland

Abstract: The functional gastrointestinal diseases (FGIDs) are often noticed disturbances. Functional dyspepsja (FD) is the most frequent FGID of the upper part of the gastrointestinal tract while irritable bowel syndrome (IBS) occurs in the lower gastrointestinal part.
Both clinical entities are characterized by rich symptomatology and the patern of the diagnostic guidelines. Recognition and the classification of FGIDs are difficult, consisting in exclusion of all possible organic disorders and subordinating on the predominant symptom basis to most appropriate class, acording to Rome III classification.
The present FGIDs pharmacotherapy is limited mostly to the symptomatical treatment and it is based on medicines conventionally used in various gastrointestinal organic illnesses (antisecretory, gastroprotective agents, antidiarrhoeal and laxative drugs). Some of them which seem to diminish visceral hypersensitivity acting *via* serotonin receptors are also used, including 5-HT_4 agonists and 5-HT_3 antagonists. Many investigations over the new causal acting medicines last at present, which would be able to abolish the main pathophysiological FD and IBS mechanisms: visceral hypersensitivity and both myoelectrical and dysmotility phenomena. Thus, new pharmacological agents influencing opioid, purinergic, NMDA, CCK-A, or NK receptors are studied.
The article is the mini-review, representing classification and the outline of the FGIDs pathogenesis, the present concepts of their pharmacological treatment and the future perspectives of pharmacoherapy with the use of new, interfering into key pathomechanisms drugs .

Keywords: functional gastrointestinal disorders (FGIDs), functional dyspepsia (FD), irritable bowel syndrome (IBS), future FGIDs pharmacotherapeutical options

Abbreviations: 5-HT – 5-hydroxytryptamine, serotonin, **Ach** – acetylcholine, **CCK** – cholecystokinin, **CLC2** – chloride channel 2, **CNS** – central nervous system, **CRF** – corticotropin releasing factor, **DLD** – dysmotility-like dyspepsia, **ENS** – enteric nervous system, **EPAN** – extrinsic primary afferent neurons, **EPS** – epigastric pain syndrome, **FD** – functional dyspepsia, **FGIDs** – functional gastrointestinal disorders, **GIT** – gastrointestinal tract, **Hp –** Helicobacter pylori, **HPA** – hypophysis-pituitary-adrenal (axis), **IBS** – irritable bowel syndrome, **IPAN** – intrinsic primary afferent neurons, **MT** – melatonin, **NK** – neurokinin, **NMDA** – N-methyl-D-aspartic acid, **P2X** – purinergic receptor, **PDS** – postprandial distress syndrome, **SST** – somatostatin, **ULD** – ulcer-like dyspepsia

The Functional Gastrointestinal Disorders FGIDs classification

The definition of the functional gastrointestinal disorder (FGID) is applied to the description of gastrointestinal symptoms, suggesting incidence of organic disease, however, without morphological changes which could be responsible for felt ailments. FGIDs are affirmed in patients with both upper and lower gastrointestinal tract symptoms. These diseases are characterized by the occurrence of various dyspeptic, dysmotility and pain symptoms, imitating organic background of observed changes. However, their recognition requires exclusion of the organic disorder which could be the cause of these symptoms. The complexity of FGIDs symptomatology created the necessity of their classification arrangement, based on pathophysiological-anatomical criteria. In 1991 experts team created The Committee to Gastrointestinal Functional Diseases and they introduced the first FGIDs classification (Rome I) which was updated and replenished about new guidelines, diagnostic criteria and patern of therapeutic conducts in definite individuals

* Corresponding author: e-mail: lukaszd@mp.pl

in 1999. Since this year, Roman Criteria II were regarded to be the most common accepted consensus, applied in everyday clinical practice and scientific investigations.

Rome II classification favored 7 principal FGIDs groups: functional disorders of esophagus, stomach and duodenum, intestines, the functional stomach pain, the bile tract dysfunctions, the functional disorders of the rectum and functional pediatric diseases. In every group, the next subclasses are distinguished, according to the predominant symptom and in relationship with this suggested pathophysiological background (1).

The Rome II guidelines found necessity of occurrence in 12 months span previous FGIDs recognition (lasting for the least 12 weeks in the period of the observation), definite ailments about the predominant character, allowing to the accomplishment of patient to one from distinguished groups qualification (1).

The progress of medical knowledge, which happened during last years in pathophysiology, diagnosing and the treatment of the functional gastrointestinal diseases together with the existing interpretative divergences caused the necessity of Rome II guidelines reanalysis. The new Rome III classification, based on updated Roman II one, was announced in year 2006. The Rome III criteria, favors 28 FGIDs disturbances in adults and 17 pediatric figures. Similarly as in Rome II classification, it is based on predominant symptoms present in particular patients without different organic disorders. However, certain histological changes were demonstrated last years in some FGIDs; therefore it questioned their only functional character. At present, according to Rome III arragement, FGIDs are divided into 8 main groups: 6 for adults and 2 for children. When compared to the previous Rome II, principal changes were introduced in B class (containing gastroduodenal disturbances) and F class related to the rectal functional illnesses. The E class (describing the functional disorders of bile tract) was also widen and the completely new division of the hitherto existing class G (Rome II pediatric FGIDs) was executed, distributing it on two classes G (neonates and babies) and H (children and adolescents). The next change in Rome III consensus, in the comparison to previous Rome II directives is the time of symptoms duration. Nowadays, it is recommended to get in the diagnostic process the confirmation of the FGIDs symptoms occurrence by 6 months previous to the recognition. Additionally, they should be kept in active form for 3 months. Moreover, one of the most important changes, introduced in Rome III criteria, was a new functional dyspepsia (FD) categorization into the postprandial distress syndrome (PDS) and the epigastric pain syndrome (EPS). PDS substituted the earlier used dysmotility-like dyspepsia (DLD) term, while EPS replaced previously distinguished ulcer-like dyspepsia (ULD) (2, 3).

The epidemiology of the functional gastrointestinal diseases

The epidemiological data show that the frequency of FGIDs occurrence is similar both in the Western and Central Europe countries and in the USA with lower incidence in Asiatic region. Among all functional diseases, functional dyspepsja (FD) and the irritable bowel syndrome (IBS) are the two most frequent clinical cases. Functional dyspepsja occurs particularly often. Estimating generally, the frequency of the FD occurrence is between 11.5-29.2%. About 20% inhabitants of Europe and USA suffer from the dyspeptic complaints and pharmacotherapy was applied in 50% of all of them by the general practitioners. The postprandial distress syndrome (previously identified as dysmotility-like dyspepsia – DLD) occurs mainly in adult patients, usually in the age below 59 years. The epigastric pain syndrome (in the former nomenclature identified with ulcer-like-dyspepsia, ULC) is often observed in patients close to 40 years. Thus, the top of FGIDs clinical manifestation falls on 40-50 year of the life. The majority of studies did not show the differences in the frequency of FD occurence in men and women, although several investigations revealed an increased FD incidence in females, especially with neurotic disturbances. In the analysis of influence of the potential risk factors on the FD occurrence, essential differences were not found for smoking, increased alcohol intake, applying vegetarian diet, or excessive drinking of coffee or strong tea. FD attended with the equal frequency in patients exhibited and not exposed on exchanged factors. There were also no differences in FD occurrence in persons with various socio-economical status. Taking under consideration the influence of non-steroidal antiinflammatory drugs (NSAID), the enlarged EPS frequency was discovered in patients taking these preparations regularly. The influence of the *Helicobacter pylori* (Hp) infection was ambiguous. In the study published in 2000, it was discovered that among patients with the evidences of Hp infection (without coexisting organic changes), 44% of them felt the dyspeptic ailments in the comparison with 36% with the negative Hp status. However, other reports also exist, supporting the thesis that Hp is not the essential risk factor of the FD development. This research subject is still

explored and numerous investigations dedicated to the influence of the Hp infection on FD and other gastrointestinal disorders development are conducted (3, 4).

The irritable bowel syndrome (IBS) is the next most common functional disorder. This syndrome occurs in about 10-15 % the adult European population, athough the epidemiological data are various depending on accepted diagnostic criteria (some reports give even 30% IBS incidence). IBS is defined as the functional disease with chronic or recurrent lower abdominal discomfort together with consipation/diarrhoea and bloating which do not have the organic background [acc. to Patterson et al. (5)]. There are also Manning's criteria, especially useful in the common ambulatory practice in IBS diagnostic procedure. They include the features which occur in the changing combination in IBS patients: the abdominal pain relieved by defecation, the changes of the defecation rhythm together with the feeling of the incomplete defecation, the feeling of rectal distension and the presence of mucus in feces (1-3).

In the case of every FGIDs, alarming symptoms suggesting the serious organic disease, such as: the loss body weight, anemia development, chronic fever, family gastrointestinal cancer occurrence in medical anamnesis, the non-specific inflammatory intestinal diseases can not accompany functional dyspeptic or intestinal symptoms. One should also keep the special caution in IBS and FD diagnosing in patients in the age above 50 (5, 6).

Pathophysiology of the gastrointestinal functional diseases

Genetic predispositions

Genetic factors may predispose some patients to the FGIDs development although their clinical expression depends on various environmental factors. The role of genetic factors may be seen in reducing the antiinflammatory cytokin (Il-10, TGF-β) level, what was affirmed in IBS patients. The decrease of antiphlogistic cytokin may result in enlarged intestinal sensitization. Moreover, in IBS patients genetic polymorphism associated with the proteins of the synaptic serotonin reuptake system was discovered, as well as the polymorphism of adrenergic alpha receptor which affects the intestinal motility. The family incidence of the FGIDs occurrence is also observed and this fact additionally underlines their potential genetic predispositions. The genetic-induced differences of the axis hypothalamus-pituitary-adrenal (HPA) glands activity are also interesting findings – in IBS patients the hyperreactivity of the HPA axis was observed (2).

Psycho-social factors

The investigation over the influence of psychosocial factors in FGIDs patients revealed that stress is the factor sharpening the FGIDs course. In FGIDs patients, especially with IBS ones, enlarged emotional and neurotic lability is usually observed, contributing to functional gastrointestinal changes as a result of the central influence on the enteric innervations. The sharp stress is the recognized factor changing motor and secretory activity of the gastrointestinal tract through neuroendocrine mechanisms. The influence of the chronic stress on the FGIDs development is not so obvious, because of the fact that chronic gastrointestinal ailments felt by the patient can be the cause of the observed neurotic disturbances. The larger intensification of anxiety, depressive and neurosis disorders marks patients with FGIDs without all doubts. This finding is consistent with the hypothesis of visceral hypersensitivity described further. However, the relationship between neuropsychiatric disorders and the FGIDs symptoms is not so visible in FD patients like in patients with IBS (2, 7).

The influence of the bacterial flora

The influence of *Helicobacter pylori* (Hp) infection in the FGIDs pathogenesis is often an explored problem at present, especially in FD. Large epidemiological investigations showed the enlarged incidence of the Hp infection in patients with ulcer-like dyspepsia (Rome II) – epigastric pain syndrome (Rome III) in the comparison to the healthy control, although when studying the patients with the PDS such dependence was not revealed. Thus, there is still no agreement with the opinion confirming the essential Hp influence on the FGIDs development. The proofs confirming the undeniable Hp role in FGIDs pathogenesis exsist. It is known that the Hp changes APUD gastric neuroendocrine cells density (mainly G cells (growth) and D ones (fall)) and causes an increase of the gastric secretion through before- and postprandial hypergastrinemia and the lowering of the somatostatin level. The next evidence of gastric secretion disturbances in Hp infected patients was obtained after intravenous administration of the gastrin releasing peptide (GRP) in patients with the peptic ulcer. There was almost a sixfold increase of the acid secretion in Hp positive participants when compared to patients without Hp infection. Despite these findings, there are also contraindicant results of Hp eradication on the gastric

secretion and the dyspeptic ailments which do not allow to accept the thesis about the positive eradicative treatment effects (8-10).

There are also reports that the excessive colonization of the lower part of the gastrointestinal tract (GIT) with the non-physiological bacterial flora disposes to the IBS development. The improvement of intestinal symptoms in response to *Bifidobacter infantis* administration, as a result of the proinflammatory Il-12 level decrease and the increase of the antiinflammatory Il-10 was observed in one of the research study. The problem of the both probiotics and prebiotics influence, is now widely discussed. It seems that they could be used as the modulators of the pharmacological therapy, although it requires further studies (11).

Disturbances of the paracrine gastrointestinal activity, the development of local inflammatory reaction and enteric nervous system dysfunction

In patients with FGIDs, the enlarged activity of inflammatory cells in the gastrointestinal wall and the increased proinflammatory cytokins level were revealed. Moreover, in about 1/3 of patients suffering from FD or IBS, the convergence of the FGIDs development and the experienced sharp inflammable episode was confirmed. It seems very probable that even chronic subinflammatory condition contributes to visceral hypersensitivity in FGIDs patients.

An increase of the neurotensin, as well as cholecystokinin and gastrin with a decrease of secretin and vasoactive peptide secretion was proved in IBS patients. The IBS patients were also characterized by intensive mastocytes and lymphocytes infiltration of intestinal wall. It resulted in enlarged histamine, methylhistamine and tryptase intestinal wall increase. What is also of essential meaning, mastocytes and other inflammatory state cells were found nearly the submucosal plexus. Neurons of this structure may be stimulated through the inflammatory mediators, released from the inflammatory cells. The suspected neuroendocrine interactions between the inflammatory mediators and the afferent endings are regarded to be factors contributing to the primary visceral hypersensitivity development (11, 12). The submucosal plexus together with myenteric one are parts of the enteric nervous system (ENS). The ENS has extremely complex structure, containing lots of different neurons connected by internal junctions and creating connections with the neurons of external autonomic innervation. ENS, acting *via* releasing many neurotransmitors, plays essential role in gastrointestinal motility, secretion and absorption. The special attention is paid to the afferent part of ENS (especially to intrinsic primary afferent neurons; IPAN which play major role in local intestinal reflexes generation and extrinsic primary afferent neurons; EPAN, which modulate gastrointestinal functions *via* central pathways). This afferent system is regarded to be coresponsible for visceral hypersensitivity and local neurogenic inflammation development (12, 13). The brief description of ENS neurons is given in Table 1 and the neuronal organizaton in gastrointestinal wall is presented in Figure 1.

Disturbances of the gastrointestinal tract motility

In healthy subjects, strong emotions or environmental stress lead to an increase of the GIT motility. In FGIDs patients, the stronger motility response in comparison to the healthy controls in similar conditions was observed. The metaanalysis of 17 cohortal investigations conducted in 2000 showed the essential delay of gastric emptying in almost 40% FD patients. The lack of the postprandial accommodation of the proximal stomach is the next characteristic dysmotility finding in patients with postprandial distress syndrome. Gastric scintigraphy, ultrasonography and barostatic measurements showed the disturbed intragastric food distribution in PDS patients, with the accumulation of gastric content in the distal stomach together with the reduced relaxation of the antral region. Duodenal dysmotility is the next pathological alternative in FD and IBS patients. These pathological changes may arise from the disturbed myoelectrical activity which is the key organizer of the gastrointestinal motor activity. Gastric dysrhythmias (both brady- and tachyarrhythmias) were disclosed in electrogastrographic (EGG) studies, with a decrease of the physiological gastric slow wave time and the lack of suspected postprandial amplitude power increase. All those observations confirm dependence between the early satiety, nausea and vomiting in FD patients and dysmotility of the upper gastrointestinal tract (2, 10, 13).

Visceral hypersensitivity

The visceral hypersensitivity is proposed as a key hypothesis, explaining the development of functional gastrointestinal diseases. This phenomenon is based on the altered peripheral mechanisms. Visceral sensations are transmitted from GIT to the brain, where the pain sensations are perceived. The enhanced central pain perception may arise from an increased signal from the gut, the ampflication of a

normal GIT signal during its travel through the spinal cord and brainstem (14, 15). An interesting observation accomplished in FD subpopulation was demonstrating enlarged sensibility to isobaric or isovolumetric balloon distention of the proximal stomach together with the epigastric pain. The increased susceptibility of the stomach wall on the expansion indicates the dysfunction of the afferent activity. There are also studies suggesting the role of distal stomach hypersensitivity in the pathogenesis of the dyspeptic ailments. Thus, the generalized disturbed gastric afferents activity may be responsible for producing the dyspeptic symptoms. Similar results in the balloon test with distal colon extension was showed in IBS patients. Moreover, FD subjects were also characterized by the intensive motility response after intestinal chemoreceptors stimulations. The intraduodenal application of the acid solution caused the nausea and the reduced duodenal motility, resulting in effective decrease of the exogenous acid clearance. Both IBS or FD symptoms are known to occur after irritation of the gut by infectious agents, after rectal instillation of glycerol, while they may be diminished by rectal administration of lidocaine (15). It is probable that visceral hypersensitivity is not the regional mechanism, occuring only in the seperated fragment of the gastrointestinal tract, but it is the generalized phenomenon. Somatic hypersensitivity as an accompanied phenomenon (estimated by a cold-water tolerance test) was identified in about 30-50% of FGIDs patients. The mechanism of visceral hypersensitivity is also associated with central mechanisms. Studies of both visceral and somatic pain have demonstrated brain regions involved in the affective, cognitive and emotional aspects of pain experience which are also connected with autonomic nervous system centers. It is likely that the perception of peripheral changes from the GIT are filtered and modulated by central mechanisms, including central amplification at the level of the spinal cord or the brain. The cortico-limbic-pontine brain regions are the crucial central part of the enhanced perception of peripheral stimuli. Moreover, the dependence between neuroticism and psychiatric disorders is observed. The possible reciprocal interaction may exist between psychosocial factors and GIT sensorimotor function; the reciprocal connection between the brain and the gut (brain-gut axis). This hypothesis implicates that psychological factors may influence gastrointestinal sensitivity. The idea of the bidirectional communication system between the enteric nervous system and the central nervous system (see Figure 2) is a key target of future FGIDs treatment. The ENS and CNS communicate through neural (autonomic nervous system), neuroendocrine (HPA axis) and neu-

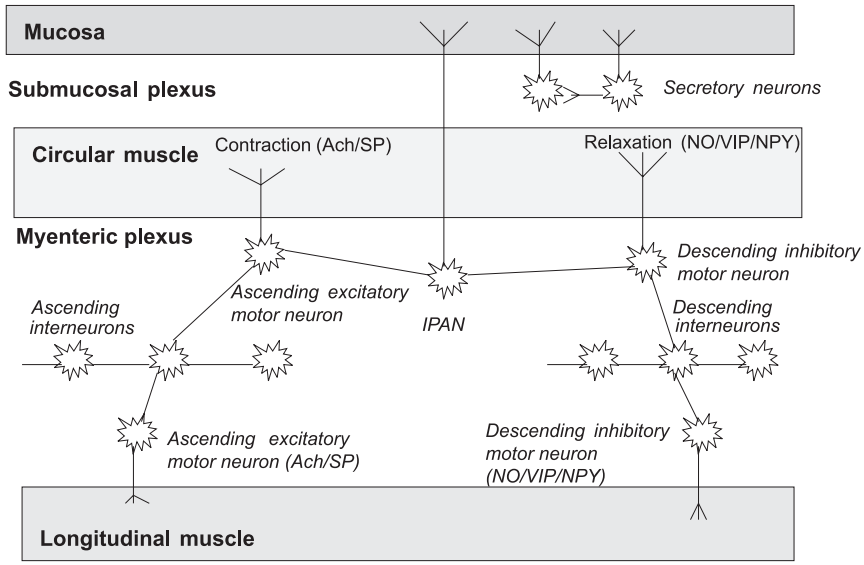

Figure 1. The diagram of ENS structure

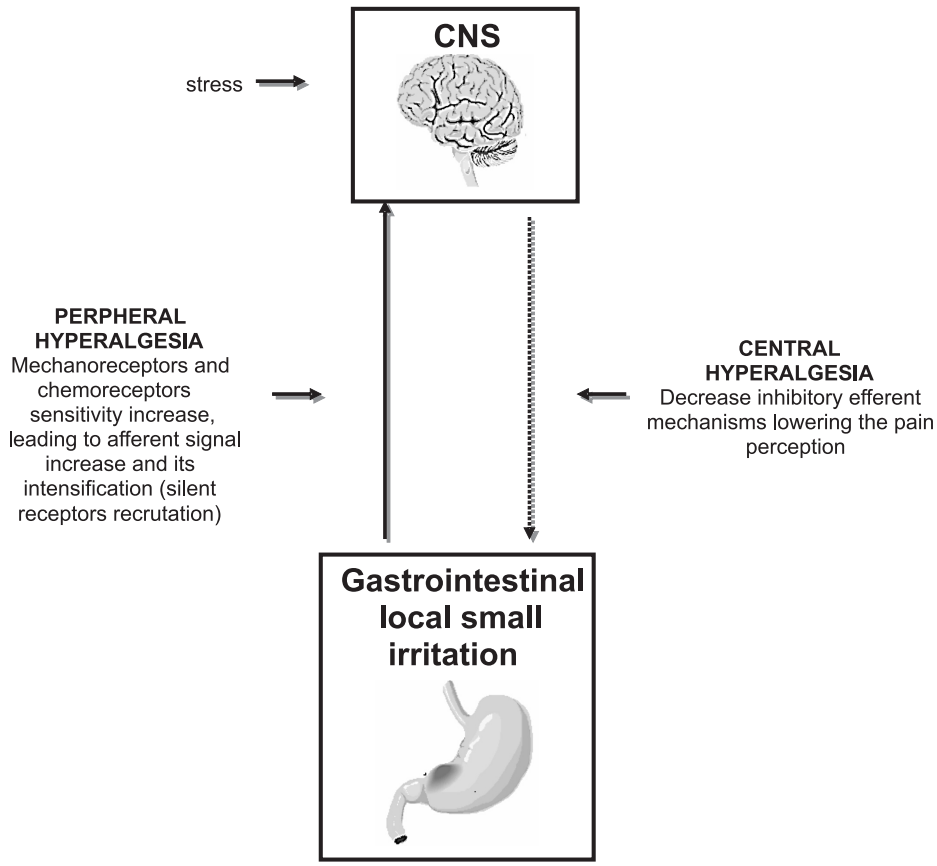

Figure 2. Visceral hyperalgesia diagram

roimmune pathways which may interact mutually. Gastrointestinal sensory information is transmitted to CNS through vagal and spinal afferent nerves while central descending nerves include both excitatory and inhibitory pathways. The plurality of various neuromediators involved in brain-gut axis functioning enables new pharmacological points of interest. Moreover, the afferent endings play an additional secretory role – they release many modulatory compounds which act *via* paracrine and autocrine mechanisms, leading to local neurogenic inflammation development and lowering the pain threshold (16). It has been demonstrated that upregulation of P2X, NMDA, AMPA, neurokinin (NK) or capsaicin (TRPV1) receptors play an importamt role in both central and peripheral hypersensitivity (16, 17). Thus, in close FGIDs future therapy, acting or blocking agents of new discovered receptors situated in peripheral or central part of the brain-gut axis are expected to be introduced in clinical practice. They are briefly mentioned further.

Table 2 represents the recapitulation of pathogenesis factors playing the part in the FGIDS development.

The symptomatology of the functional gastrointestinal disorders

The FGIDs symptomatology is very rich. FGIDs of the upper part of the gastrointestinal tract are characterized by pyrosis, non cardiac chest pain, epigastric pain (symptom predominant in EPS), the feeling of postprandial fullnes after even small meal, belching, nausea and vomiting (particularly in PDS). According to Rome III criteria, these complaints should appear 6 months and last by 3 months before

Table 1. The most important neurons and chemical neurotransmission in the enteric nervous system (ENS) (13, 14)

ENS neuron	Neurotransmiter	Function
IPAN (Intrinsic Primary Afferent Neurons)	Acetylcholine	Activated by mechanic or chemical stimuli, initiate peristaltic and secretory reflexes
EPAN (Extrinsic Primary Afferent Neurons);	Acetylcholine	Central pain perception emotional and behavioral pain perception components
Ascending myoenteric neurons	Acetylcholine, Substance P	Activate ascending motor neurons
Descending myoenteric neurons ,	Acetylcholine, Substance P, ATP	Activate descending myoenteric motor neurons
Ascending (excitatory) myoenteric	Acetylcholine, Substance P	Triggering contraction of smooth muscle motor neurons proximal to their cells bodies *via* muscarinic M_3 and NK1 receptors
Descending (inhibitory) myoenteric motor neurons	Vasoactive intestinal peptide, Nitric oxide, Neuropeptide Y, ATP, GABA	Triggering relaxation of smooth muscle distal to their cells bodies
Submucosal ganglion neurons	Acetylcholine	Elicit vasodilatation and glandular secretion
Modulatory myoenteric neurons	Serotonin	Elicit presynaptic activation of acetylocholine release *via* D_2 receptors
Modulatory myoenteric neurons	Dopamine	Elicit presynaptic inhibition of acetylocholine release *via* 5-HT_4 receptors
Enterochromatoffin cells	Serotonin	Activate IPANs *via* 5-HT_3 receptors
Interstitial cells of Cajal	Nitric oxide	Mediate influence of ENS neurons on smooth muscle, organize myoelectrical activity

Table 2. Proposed pathomechanisms contributing to the functional gastrointestinal disorders (FGIDs) development

Gastrointestinal dysmotility	• Postprandial antral motility decrease • Gastric fundus relaxation decrease • Gastric emptying rate decrease • Gastric myoelectrical activity decrease
Visceral hypersensitivity, ENS disturbances	• Increased perception to gastrointestinal wall stretching • Increased sensitivity to chemical stimulation • Chronic inflammatory reaction development
Acid hypersecretion	
Helicobacter pylori infection	• Acid hypersecretion • Neuroendocrine cells density alternation • Dysmotility ???
Stress	• Acute stress • Chronic stress ???
Psychiatric disturbances	• Anxiety disorders • Depressive disorders • Neurotic disturbances
Genetic predispositions	• Family incidence of FGIDs

making the diagnosis of the gastrointestinal functional disease.

The special FGIDs figure affecting the lower part of the gastrointestinal tract is the irritable bowel syndrome (IBS). It is characterized by returning or co-exsistence combination of such symptoms as: pain of the lower abdomen, discomfort in abdominal cavity, bloating, the change of the defecation rhythm (diarrhoea or constipation) although the defecation causes the temporary improvement of felt ailments.

Table 3. Class of medicines applied in current FD pharmacotherapy

Pharmacological class	Drug examples	Effects
Hp eradicative medicines	The pattern of medicines containing: Aminopenicillin, Macrolide, PPI	Hp eradication, indirectly dysmotility improvement and secretolytic
Neutralizing agents	Magnesium salts Aluminium salts	Gastroprotection, an acid excess neutralization oraz hypothetic antiinflammatory
Bismuth salts		Gastroprotection, an auxliary agent in Hp eradication
Sucralfat		Gastroprotection, hipothetic antiinflammatory
Prokinetics	Metoclopramide, Cisapride	Prokinetic and antireflux
Proton pump inhibitors (PPI)	Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole	Antisecretory and in Hp eradication
Antihistaminic H_2 agents	Ranitidine, Famotidine	Antisecretory and partly antiinflammatory
Antidepressive drugs	Tricyclic antidepressive agents SSRI (Selective Serotonin Reuptake Inhibitors)	Tymolepic, antidepressive and anxiolytic
Anxiolytics	Benzodiazepines Buspirone	

Table 4. Class of medicines applied in current IBS pharmacotherapy

Pharmacological class	Drug examples	Pharmacological effect
Spasmolytics	Mebeverine, Scopolamine, Dicycloverine, Cymetropium, Pinaveryne	Smooth muscle relaxation through anticholinergic effect or calcium channels blockade
Antidiarrhoeal agents	Loperamid Diphenoxylat	Opioid μ and κ peripheral receptors agonists – decreasing of gastrointestinal motility and sphincter tone increasing, additionally antinociception
Laxative agents	Lactulosum	Increasing intestinal osmotic load, decreasing water reabsorption , peristaltic movement acceleration
5-HT_4 receptor agonists	Tegaserod Prucalopride	5-HT_4 receptor stimulation, increase of intestinal motility, CGRP and SP releasing – prokinetic effect in constipation-predominant IBS form
5-HT_3 receptor antagonists	Ondansetron Granisetron Alosetron	5-HT_3 receptor antagonists decreasing of ENS stimulatory neurotransmitters releasing: Ach, SP – antiemetic and antidiarrhoeic
Antidepressive agents	Serotonin Selective Reuptake Inhibitors (SSRI) Tricyclic antidepressive agents $5HT_{1A}$ receptor agonists (Buspirone)	Central antinociception
Anxiolytics		

As it was mentioned earlier, despite the validated qualitative and quantitative diagnostic features presented in Rome III policy statement, the Manning's IBS criteria still are used in the general clinical practice (they include six main features: the chronic lower abdominal pain connected with the defecation, which causes the temporary improvement ailments, diarrhoeas, constipations or mixed figure, the feeling of incomplete defecation and the distension of the rectum, mucus in the stool).

It should be noticed that the recognition of every FGIDs is done as a diagnosis by exclusion. It means, that all possible coexisting diseases which could be the cause of the ailments should be excluded in the diagnostic proceedings. It does not mean automatically, that no different organic gastrointestinal disease can accompany the functional disease in the same patient or that several functional disorders can

Table 5. New classes of medicines in FD treatment

Pharmacological class	Expected effect
Prokinetics A. Dopaminolytic Domperidone, Itopride, Levosulpiride B. Serotoninergic Mosapride, Tegaserode C. Motylin analogues Erytromycin, ABT229	D_2 receptors blockade and 5-HT_4 receptors activation. Gastric emptying rate acceleration, increasing in antrum motility, antiemetic properties
κ- Agonists Fedotozine, Asimadoline	Visceral hypersensitivity and visceral pain decrease
P2X receptor antagonists	Visceral pain decrease (Antinociception)
NMDA receptor antagonists	Visceral pain decrease (Antinociception)
Vanilloid receptor agonists	Visceral pain decrease (Antinociception)
SST receptor agonists Oktreotyd	Motility and secretion functions modulating
CCK receptor antagonists Loxiglumide	Motility increase, visceral pain decrease (Antinociception)
NK_1 receptor antagonists Aprepitant, Ezlopitant NK_2 receptor antagonists Nepadutant, Saredutant NK_3 receptor antagonists Talnetant	Strong prokinetic and antiemetic effects (Antinociception)
CRF receptor antagonists Antalarmin	Motility and secretory disturbances due to stress and HPA axis hyperreactivity modulation

not coexist at one patient. It widens considerably the symptomatology of FGIDs and make their diagnosis more difficult (2, 5, 7).

The present pharmacological approach in FD and IBS treatment

The present therapeutic options in functional dyspepsia treatment include both non-pharmacological methods (of still unproved effectiveness), and pharmacotherapy with the use of traditionally applied groups of medicines (which are administrated not only in the FD treatment, but also in other diseases of the gastrointestinal tract) (18).

Non-pharmacological methods, being the optional, additional strategy in the FD therapy include:

1. Dietetic modifications
   - Consumption of more frequent but of smaller volume meals
   - Avoidance of meals in evening and night hours
   - Limitation in consuming fatty meals
2. The psychological therapy
   - Relaxative therapies and teaching of coping with the stress
   - Behavioral therapy
   - Biofeedback
   - Hypnotherapy
3. Vegetable preparations – phytotherapy
   - Capsaicin
   - STW 5

Generally, these therapies were not subjected to the critical, unambiguous opinion, according to Evidence Based Medicine (EBM) principles. Thus, their effectiveness and applying indications are controversial. Among them, herbal preparation STW5 as the auxiliary phytomedicine is one of better standardized methods. It contains extracts from chamomile, mint, lemon balm, caraway seed and licorice. It was showed in wide conceived, doubly blinded and randomized clinical investigation, that after 8 weeks of the treatment in about 40% patients receiving STW5, the essential decrease of dyspeptic symptoms was affirmed. The exact pharmacological action of the components present in that preparation was not discovered, however, spasmolitic and anti-inflammatory effects are postulated. The results of the investigation of the capsaicin use – the active component of the chilli – are also encouraging

Table 6. New classes of medicines in IBS treatment

Pharmacological class	Expected effects	Potential application
Prokinetics A. Dopaminolytic Domperidon	Gastrointestinal motility increase (mostly upper part)	Constipation predominant IBS
B. Serotoninergic Norcisapride, Renzapride, Mozapride, Tegaserod	Gastrointestinal motility increase (mostly lower part), Antinociception	Constipation predominant IBS
C. Antiserotoninergic Alosetron, Cilansetron	5-HT_3 receptor antagonists, Gastrointestinal motility decrease	Diarrhoea predominant IBS
Cholinolytics (anticholinergic agents) Darifenacyne, Zamifenacyne	M3 receptor antagonists, lower gastrointestinal part motility decrease	Diarrhoea predominant IBS
Serotoninergic and noradrenaline agents SSRI (Selective Serotonine Reuptake Inhibitors) SNRI (Serotonine Noradrenaline Reuptake Inhibitors)	Antinociception	Both IBS forms
Opioid receptor agonists Loperamide, Fedotozine, Asimadoline	Opioid μ and κ agonists Gastrointestinal motility decrease	Diarrhoea predominant IBS
Opioid receptor antagonists Alvimopan	Opioid μ antagonists Gastrointestinal motility increase	Constipation predominant IBS
α_2 Adrenergic receptor agonists Clonidine, Lidamidine	Antinociception	Both IBS forms
CCK receptor antagonists Loxiglumide, Proglumide	CCK-A receptor antagonists Mass intestinal movements generation	Constipation predominant IBS
NMDA receptor antagonists Dizocilpine, Memantine	Antinociception	Both IBS forms
NK receptor antagonists Ezlopitant Nepadudant	NK_1 receptor antagonist, gastrointestinal motility decrease and antinociceptive effect NK_2 receptor antagonist, gastrointestinal motiliy decrease and probable antinociceptive effect	Both IBS forms
ClC-2 chloride channel activators Lubiproston	Apical chloride channels of the intestinal cells activation, gastrointestinal motility and secretion increase	Constipation predominant IBS

because its use brought the improvement in some FD patients (18-20).

The current guideline of the pharmacological FD therapy are based on the use of anti-acid neutralizing agents, gastroprotectives medicines, secretolytics, prokinetics and antidepressant together with anxiolytic drugs as supplementary medicines (especially in patients suffering from stressed emotional lability). Pharmacological *Helicobacter pylori* eradication in FD patients with positive Hp status is still controversial. The part of investigations indicates on insignificant, but the characteristic advantage resulting from the eradicative treatment, while different ones revealed lack of such effect (21-24). The traditional pharmacological interventions based on the most often applied medicines are given in Table 3.

In the second most widespread functional gastrointestinal disorder, the irritable bowel syndrome, the recommended guidelines of the therapeutic strategy also exist. The applied pharmacotherapy depends on the predominant clinical IBS feature (diarrhoea-predominant IBS, constipation-predominant IBS, mixed IBS figure). Similarly as the in the FD case, non-pharmacological and conventional treatment methods are available (25, 26).

Non-pharmacological, additional methods include:

1. Dietetic modifications
   - The diet rich with vegetables, fruits, cereal seeds
   - The diet containing wheat bran
2. The psychological therapy
   - Relaxative therapies and teaching of coping with the stress
   - Behavioral therapies
   - Biofeedback
   - Hypnotherapy
3. Application of probiotics
   - *Lactobacillus plantarum*
   - *Bifidiobacterium breve*
   - *Streptococcus faecium*

Particularly interesting seems to be the therapy with use of non-pathological microorganisms. The mechanisms explaining the partial withdrawal of intestinal ailments in patients applying probiotic preparations are only partly known and require further investigations. An increase of antiinflammatory mediators level was showed, such as Il-10, together with a decrease of proinflammatory TNF-α and Il-8 production. Moreover, probiotic bacteria showed the ability to the bile acids deconiugation (an excess of these compounds was observed in patients with diarrhoea-predominant IBS figure). The production of small-chain fatty acids, which have the ability of the induction of propulsive intestinal cramps and accelerating the intestinal transit seems to be also of essential meaning (27, 28).

Conventional IBS pharmacotherapy includes several groups of drugs, introduced in Table 4.

Current serotoninergic and non-serotoninergic targets in the pharmacotherapy of visceral hypersensitivity as major FGIDs pathophysiological factors

The most important goal of both IBS and FD present and future pharmacotherapy seems to be the visceral hypersensitivity. Several targets on afferent nerves for the treatment of visceral hypersensitivity were identified, including 5-HT_3, 5-HT_4, opioid and α-adrenergic receptors (29-31). These drugs also improve gastroduodenal motility, thus, considering their evident pharmacological effect, they are nowadays classified as prokinetics agents (and not "anti-hypersensitive" ones).

The drugs affecting the hypersensitivity phenomenon inlude limited amount of serotoninergic agents (both 5-HT_3 antagonists and 5-HT_4 agonists), such as Cisapride. It was one of the first serotoninergic agents (5-HT_4 agonist) registrated in FGIDs treatment. 5-HT_4 receptor agonists stimulate the release of neurotransmitters and increase colonic motility, providing a rationale for their use in constipation predominant IBS. The next drug – tegaserod (Zelnorm), a partial 5-HT_4 receptor agonist was approved for IBS and constipation but removed from the market in March 2007 because of cardiovascular side-effects. It has been subsequently reintroduced under an investigational new drug protocol. It was also discovered, that 5-HT_3 antagonists such as alosetron, ondansetron, granisetron modulate visceral afferent activity and may improve abdominal pain. In clinical trails these drugs were effective in diarrhoea-predominant IBS. However, alosetron was associated with ischemic colitis and serious complications related to severe constipation, prompting the Food and Drug Administration (FDA) to remove it from the market in the United States. Evaluation of post-marketing data and demand from a subset of patients who had responded to treatment has prompted the FDA to bring the drug back to the market under control (32-35). Tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRI) are also often used in patients with suspected visceral hypersensitivity. Amitriptyline in depressive FGIDs decreased visceral sensitivity but psychotherapy also improved symptoms without any change in visceral hypersensitivity. SSRI used in healthy subjects did not change sensitivity to gastric or colonic distension. Moreover, some evidence suggests that the mixed serotonin and noradrenaline reuptake inhibitors (SNRI), such as wenlafaxine, can reduce sensations during colonic distention in healthy volunteers. Thus, the results of the studies on serotoninergic antidepresants and their potential beneficial effects in FGIDs patients are still contradictory (29-31).

The next drugs widely used in IBS are mebeverine, pinaverine and trimebutine, classified as direct smooth muscle spasmolytic agents. The last one acts *via* peripheral gastroduodenal opiod receptors and modulates some neuropeptides releasing (gastrin, motilin, VIP). These drugs, similar to cisapride, increase gastroduodenal motility and additionally diminish intestinal sensitivity and affect intestinal smooth muscle relaxation. The drugs mentioned above are also included in Table 4.

The future therapeutic perspectives in functional dyspepsia and irritable bowel syndrome treatment

The present FGIDs pharmacotherapy is difficult and often does not allow the achievement of

desired effect. Because of the fact that FGIDs pathological background is very complex without the possibility of the indicating of predominant pathomechanism, the nowadays therapy has only the empirical character. Comparatively small quantity of the accessible „pharmacological basket" of medicines dedicated to applying in FGIDs is the next problem. Increasing knowledge in neurogastroenterology, structural organization and ENS function and mutual interactions between ENS and CNS, enable the new possibilities of the pharmacological approach in the FGIDs therapy. New substances acting to the influence on the brain-gut axis are now in the circle of interests (29, 36, 37).

In the functional dyspepsia treatment, (mostly in the EPS therapy), new medicines with antinociceptive properties are investigated. The κ-opioid receptor agonists are one of the promising groups of medicines. Fedotozine and Asimadoline are the studied representatives of this group and the preliminary results demonstrated the softening effect on visceral pain. The next potential action point of medicines affecting visceral hypersensitivity are other receptors situated on afferent sensory vagal and sympathetic fibres. Purinergic receptors, glutaminergic NMDA receptors, vanilloid and somatostatin ones belong to this group. Purinergic receptors P2X take part in generating the visceral pain. It was shown, that P2X antagonists were effective in reducing the visceral pain in the course of the inflammatory reaction in the animal model. The similar effect was observed after the NMDA antagonists, although dextromethorphan paradoxically caused an increase of nociception in the response to the colon expansion. Vanilloid receptors are situated on the afferent endings, stimulated by capsaicin, pH fall and the temperature change. They particularly occur in the stomach antrum, playing the suppressive role in gastric nociception. Thus, vanilloid receptor agonists may become an important pharmacological agents, administrated to diminish visceral pain. Somatostatin is the peptide modulating both the motility and secretion in the gastrointestinal tract. Somatostatin analogues (Octreotid) showed profitable effects connected with the reduction of the postprandial fullness feeling in PDS patients (36, 38).

The next interesting future pharmacological target points in the FD treatment are cholecystokinin (CCK), tachykinin (NK) and corticoliberin (CRF) receptors. Cholecystokinin is a neuropeptide released in the gastrointestinal tract mostly in the response to fatty meal. It is considered that CCK causes the strong inhibitory effect on gastric emptying (through the influence on CCK-A receptors located on afferent vagal fibers) and co-introduces the visceral pain. The phenomenon of hypersensitivity to CCK and the intensified interaction between serotoninergic and CCK neurotransmission was also discovered in FD patients. In 90% of studied patients, intensified dyspeptic effects after synthetic CCK analogue administration and their withdrawal after CCK antagonist application – loxiglumide were demonstrated. It is a strong proof convincing that CCK is the next potent pharmacological link between dyspeptic ailments and molecular pathomechanisms. Thus, CCK antagonists are seem the next promising direction in the searches of new medicines dedicated to the FD treatment. The possibility of tachykinin (substance P, neurokinin A, B – NKA, NKB) pathway modulation is a second interesting solution. Experimental investigations revealed antiemetic effects of the NK-1 antagonist – aprepitant. It gives the hope to the future application of this drug as antiemetic medicine during the cytostatics treatment in neoplastic patients. Moreover, NK-1 antagonists also have antinociceptive effects and probably possess other additional influences on the gastrointestinal motor activity (36, 38).

The modulating influence of the brain-gut axis was also found as the next pharmacological target point. The activation of the HPA axis by comprehended wide stress factors contributes to the development of dyspeptic disorders. The HPA hyperactivity was discovered in the FGIDs course what was associated with the raised proinflammatory cytokin level. Thus, the corticotropin (CRF) receptor antagonists make up the next alternative of the functional diseases treatment, especially these ones occuring as a result of the excessive reaction on numerous environmental stressors (36, 38).

The present research studies are also concentrated on new prokinetic agents discovery. They would broaden the arsenal of medicines applied mostly in PDS. The investigations aimed to motilin receptors agonists are of the the special attention. The prokinetic effect of erythromycin is known since many years, because gastric emptying acceleration during the erythromycin treatment was observed. The new erythromycin analouges (ABT229) also show the prokinetic effect. Other medicines working *via* different mechanisms – especially through the influence on dopaminergic and serotoninergic neurotransmition are studied. Itoprid is dopaminergic D_2 receptor antagonist which also reveals the properties of acetylcholinoesterase inhibitor. It has antiemetic and gastric emptying acceleration properties. Sulpiride derivative, levo-

sulpiride, is also the D_2 antagonist with an additional agonistic effect to the 5-HT_4 receptor. It accelerates gastric emptying and intensifies antrum motility together with reducing visceral hypersensitivity. The next studied agents – Mosaprid is 5-HT_4 agonist and 5-HT_3 antagonist with the action profile similar to levosulpiride. (36, 38).

Some of pharmacological subjects presented above are also studied as new therapeutic options in the IBS treatment. Special expectations are connected with the new agents affecting the gastrointestinal motility. In dependence to IBS figure (with predominant diarrhoea or constipation), new substances reducing or increasing the gastrointestinal motility are searched. Regardless to predominant IBS symptom, new spasmolytic medicines and agents reducing the visceral pain seem to be applied in novel IBS therapy (39, 40).

The recapitulation of new classes of the medicines mentioned above which can find the use in the future dyspepsia treatment is given in Table 5, while Table 6 reports the classes of new medicines being in clinical investigations in the IBS treatment.

On the margin, it should be also mentioned about the potential melatonin (MT) use in the IBS treatment. Some studies exist confirming sleep disturbances in part of the IBS patients. They also report night gastrointestinal complaints. In this subpopulation a hypothesis may be done that quantitative (and maybe qualitative) sleep disorders may be a cause of FGIDs. In one study, melatonin treatment in IBS patients with co-exsisting dyssomnia was introduced getting very promising improvement of IBS ailments. Thus, MT also seems to be the potential auxiliary medicine, normalizing the disturbed activity of gastrointestinal tract, secondary to the dyssomnia (41, 42).

Gastroprotective melatonin effect in DLD patients (at present EPS patients) was also studied showing its effectiveness in the appeasement of pain and dyspeptic ailments. It is known that MT is deposited in large quantities in neuroendocrine gastrointestinal cells, and it has antioxidative (neutralizing free oxygen radicals) and the gastroprotective (connected with the PGE induction synthesis) properties. Moreover, melatonin through influence on its MT2 receptors stimulates the bicarbonates production, showing neutralizating effect in the night acid overproduction in dyspeptic patients (43).

The exact mechanism of melatonin action related to FD and IBS symptoms improvement is still unknown. That is why these results are still treated as preliminary ones, requiring further investigations. However, the melatonin seems to be the auxiliary drug, normalizing the gastrointestinal function.

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