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The Effectiveness of Add-on Treatment with Nutraceutical "Standard Zdorovia: Gastro" in Patients with Irritable Bowel Syndrome

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Aim: evaluation of the effectiveness of the nutraceutical "Standard Zdorovia: Gastro" ("SZ Gastro") in the treatment of patients with irritable bowel syndrome (IBS).
Materials and methods. 52 patients (62 % women) diagnosed with IBS and IBS in combination with functional dyspepsia (FD) were included in the study and divided into two groups. Both groups received basic therapy according to the guidelines. The experimental group received as add-on the nutraceutical "SZ Gastro" (containing a standardized amount of menthol, gingerol and D-limonene); patients in the control group — placebo. The duration of the study was 30 days. The severity of somatic symptoms was assessed with the 7×7 questionnaire. Emotional state was assessed with the Four Dimensional Distress, Depression, Anxiety, and Somatization Questionnaire (4DSQ).
Results. Patients of the experimental and control groups did not differ from each other either in terms of demographics, basic treatment, or in the severity of symptoms at the beginning of the study.
The effectiveness of the treatment in the patients, who received add-on "SZ Gastro" was significantly higher than in the patients of the control group: in the control group the percentage of improvement of somatic symptoms was 22.35 %, in the experimental group it amounted to 49.18 % (χ^2 = 15.9; p = 0.0001). The percentage of patients with significant decrease of emotional disturbances was also higher in the experimental group: distress (χ^2 = 18.7; p = 0.0000), anxiety (χ^2 = 6.9; p = 0.0097) and somatization (χ^2 = 14.99; p = 0.0001). No significant side effects were registered in any of the groups.
Conclusions. Add-on of nutraceutical "SZ Gastro" to basic treatment is safe and significantly increases effectiveness of the therapy in the patients with IBS and IBS in combination with PD.
Keywords: irritable bowel syndrome, functional dyspepsia, dietary supplement, menthol, gingerol, limonene, treatment
Conflict of interest: The authors declare no conflict of interest.

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Эффективность включения нутрицевтического препарата «Стандарт Здоровья: Гастро» в схему лечения пациентов с синдромом раздраженного кишечника

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Цель исследования. Оценка эффективности нутрицевтического препарата «Стандарт Здоровья: Гастро» («СЗ Гастро») в терапии пациентов с СРК.

Материалы и методы. 52 пациента (62 % женщины) с диагнозом СРК и СРК в сочетании с функциональной диспепсией (ФД) были включены в исследование и распределены в две группы. Пациенты основной группы в дополнение к стандартной терапии получали нутрицевтический препарат «СЗ Гастро» (содержащий стандартизированное количество ментола, гингерола и D-лимонена); пациенты контрольной группы — плацебо. Продолжительность исследования составила 30 дней. Оценка выраженности соматических симптомов проводилась с помощью опросника «7×7». Психоэмоциональное состояние оценивалось при помощи «Четырехмерного опросника Дистресса, Депрессии, Тревоги и Соматизации» (4DSQ).

Результаты. Пациенты основной и контрольной групп статистически значимо не отличались друг от друга ни по демографическим показателям, ни по компонентам базовой терапевтической схемы, ни по выраженности симптомов функциональных нарушений и психоэмоциональных расстройств перед началом терапии. Эффективность терапии у пациентов, получавших стандартную терапию и «СЗ Гастро», оказалась достоверно выше, чем в группе пациентов, получавших стандартную терапию в сочетании с плацебо: если в контрольной группе процент улучшения соматических симптомов составлял 22,35 %, то у пациентов, принимавших «СЗ Гастро», он составил 49,18 % (χ^2 = 15,9; p = 0,0001). Процент пациентов, у которых на фоне терапии купировались признаки дистресса (χ^2 = 18,7; p = 0,0000), тревоги (χ^2 = 6,9; p = 0,0097) и соматизации (χ^2 = 14,99; p = 0,0001), был также значимо выше в основной группе. Ни в одной из групп не было зарегистрировано выраженных побочных эффектов проводимого лечения.

Выводы. Включение в схему стандартной терапии пациентов с СРК и СРК в сочетании с ФД нутрицевтического препарата «СЗ Гастро» достоверно увеличивало эффективность проводимой терапии за счет уменьшения выраженности соматических симптомов и эмоциональных нарушений, а также не приводило к развитию побочных явлений.

Ключевые слова: синдром раздраженного кишечника, функциональная диспепсия, биологически активная добавка, ментол, гингерол, лимонен, лечение

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Introduction

Irritable bowel syndrome (IBS) is one of the most common functional diseases of the gastrointestinal tract (GIT). The prevalence of IBS in the population is 10–13 % [1]. The disease significantly impairs the quality of life and limits their social activity of such patients [2].

An important feature of IBS is its high frequency of joint presence of other variants of functional GIT disorders and emotional disturbances [3–7]. In a significant percentage of cases (from 27 to 83 %), IBS is combined with symptoms of functional dyspepsia (FD) [3, 5]. Patients with IBS have a high (10 to 40 %) level of comorbidity with anxiety and depression, as well as the increased level of psychological distress (negative and pathogenic forms of stress) [4, 6–8]. At the same time, emotional disorders in IBS often show unidirectional dynamics with the severity of somatic symptoms, what allows us to consider them as one of the important factors of impact on the course of the disease [8, 9].

Despite the significant number of efforts, the effectiveness of therapy for IBS is still insufficient, and approaches to the treatment of combined functional disorders of the gastrointestinal tract (for example, IBS and FD) have not been developed. The chance of resolution of IBS symptoms at 12–20 months follow-up is only 38 % [10].

Administration of psychotropic drugs to patients with functional diseases of GIT can lead to an increase in the duration of remission. However, it is associated with a high withdrawal rate due to side effects and prejudices [11].

A possible way to improve the effectiveness of IBS therapy may be the inclusion in the treatment regimen of nutraceutical preparations ("nutrition" (nutrition) and "pharmaceutical" (pharmaceutical drug)) [12], containing natural active substances that have multidirectional activity, what means can address multidimensional pathogenetic mechanisms of this disease. At the same time, the nutraceutical drugs most often do not cause objections due to the high loyalty of patients to "natural, herbal" substances.

Nutraceuticals are food products and their components that have a positive effect on human health, including the prevention and treatment of diseases. Nutraceuticals include healthy and functional foods, as well as biologically active food supplements [13].

"Standard Zdorovia: Gastro" ("SZ Gastro") is a nutraceutical preparation based on peppermint and ginger oils, containing standardized amounts of active ingredients: menthol (80mg), D-limonene (5mg) and gingerol (7mg).

Peppermint oil is included in the recommendations for the treatment of IBS developed by the World Gastroenterological Organization, as well as in the Rome IV criteria [1, 14]. Its effectiveness in reducing the symptoms of IBS and, in particular, abdominal pain has been shown in a large number of studies [15, 16].

The main active ingredient in peppermint is menthol. Menthol has anti-inflammatory, analgesic and antispasmodic effects [17, 18]. In addition, in a study by Imai et al. it has been shown that menthol helps to restore the composition of the intestinal microbiota [19]. Mint's anti-anxiety and antidepressant effects have also been linked to menthol [20].

Another active component of peppermint, D-limonene, helps to restore the function of the mucosal barrier of the gastrointestinal tract and protect the gastric mucosa from the aggressive effects of hydrochloric acid [21, 22].

Gingerol, the active component of ginger extract, has antioxidant, anti-inflammatory, and antimicrobial properties, and also normalizes gastrointestinal motility [23]. For example, in a study by Ghayur et al. the antispasmodic effect of gingerol has been noted [23, 24]; a number of works provide evidence of its prokinetic action [24, 25]. Gingerol is also known to increase the production of digestive enzymes such as trypsin and pancreatic lipase [26]. Gingerol is able to penetrate the blood-brain barrier (BBB) through passive transport [27]. Due to its effect on serotonin receptors localized in the central nervous system, it has an anti-anxiety and antidepressant effect [28].

Thus, the complex effect of the active components of "SZ Gastro" helps to reduce both somatic and emotional symptoms in patients with IBS. Previously, we published the results of a study that confirmed that the inclusion of the nutraceutical drug "SZ Gastro" in the regimen of standard therapy leads to an increase in the effectiveness of standard therapy, possibly due, among other things, to changes in the intestinal microbiome and metabolome [29].

Objective

The aim of this study was to evaluate the effectiveness add-on of the "SZ Gastro" to basic treatment scheme for patients with IBS and IBS combined with FD in relation to somatic and emotional symptoms.

Materials and methods

We planned to include at least 50 patients with a confirmed diagnosis of IBS and IBS in combination with FD. The recruitment of patients was carried out in the Clinic of propaedeutics of internal diseases, gastroenterology and hepatology. V.Kh. Vasilenko of the First Moscow State Medical University named after I.M. Sechenov. Clinical diagnoses were established in full accordance with the recommendations of the Russian Gastroenterological Association (RGA) and the Association of Coloproctologists of Russia (ARC) for the diagnosis and treatment of irritable bowel syndrome, and the recommendations of the RGA for the treatment of patients with functional dyspepsia [30, 31].

All patients who were included in the study signed the informed consent and filled out an individual registration card. The study was approved by the ethics committee of the Federal State Budgetary Scientific Institution NTSPZ (No. 501 dated February 05, 2019).

The study included adult patients form 18 and to 59 years of age, patients with organic bowel disease, renal, hepatic insufficiency and mental illness that significantly impairs self-report (schizophrenia, bipolar disorder, epilepsy).

The study design was a double-blind, placebo-controlled. In the experimental group, patients for 30 days in addition to their basic therapy received the nutraceutical "SZ Gastro" 1 capsule (730 mg) once a day during breakfast; in the control group, in addition to the basic therapy, — capsule with placebo (olive oil capsule) with a similar dosing regimen.

Basic pharmacological treatment for patients in the control and experimental groups was carried out in accordance with published recommendations [30, 31].

Research methods

Patients were examined by gastroenterologists, psychiatrists and clinical psychologists.

Evaluation of the intensity of functional gastroenterological symptoms

The 7×7 Questionnaire [32] was used to determine the intensity of IBS and FD symptoms. The questionnaire included seven main symptoms characteristic of these diseases: epigastric pain, epigastric burning and fullness, early satiety, abdominal pain, bloating, and disturbances in stool consistency and/or frequency. The main indicator of the presence and intensity of symptoms is the "Total score", which is the sum of the scores of all symptoms at baseline and during treatment.

Assessment of emotional disturbances

The psychological state of the patients was assessed using the Four-Dimensional Distress, Depression, Anxiety, and Somatization Questionnaire (4DSQ) [33]. 4DSQ is a self-questionnaire that includes 50 questions. The final indicators are the sums of points on four subscales, reflecting four types of emotional disorders. The distress score is diagnostically significant at 10 points or more; depression — 2 points or more; anxiety — 8 points or more; somatization — 10 points or more.

Statistical data processing

Statistical data processing was carried out using the Statistica 10.0 statistical software package. The non-parametric Mann-Whitney *U*-test was used to determine the significance of differences between groups before the start of therapy. Pearson's test of agreement (χ^2) was used to compare the effectiveness of treatment in both groups. Differences were assessed as significant at a significance level of $p < 0.05$.

To assess the severity of the reduction in somatic symptoms, based on the results of the Questionnaire "7×7", the indicator "percentage of improvement" was calculated. The percent improvement is the quotient of the difference between the mean at baseline and end of the study by the mean at baseline, taken as a percentage.

The effect of "SZ Gastro" on the psycho-emotional state of patients was determined by counting the proportion of patients whose symptoms, expressed at the beginning of the study, disappeared by the end of the study.

Results

52 patients were included and completed the study. Patients in the control and experimental groups did not statistically significantly differ in any of the parameters before the start of therapy. The severity of somatic symptoms in both groups in most cases corresponded to mild or moderate (Table 1).

The treatment scheme was similar in both groups. Patients with diarrheal and mixed variants of IBS received antispasmodics. IBS patients with constipation received antispasmodics in combination with a laxative of one of the groups (laxatives that increase the volume of feces, osmotic and stimulant laxatives).

When IBS was combined with FD, therapy with antispasmodics and proton pump inhibitors was prescribed.

Evaluation of the treatment effectiveness: somatic symptoms

The ongoing therapy in both groups led to a decrease in the intensity of symptoms. To the end of

Table 1. Characteristics of patients before the start of therapy

	SZ Gastro (*N* = 26)	**Placebo (*N* = 26)**	***p*-level**
female	15	17	ns
male	11	9	ns
IBS	18	20	ns
IBS + FD	8	6	ns
Age (years)	34,65 ± 11,98	31,69 ± 9,34	0,51
Duration IBS (months)	73,58 ± 83,56	64,42 ± 68,13	0,98
7×7 "Total score"	11,73 ± 4,85	13,77 ± 5,80	0,10
4DSQ Distress	10,92 ± 7,28	11,00 ± 7,81	0,86
4DSQ Depression	1,65 ± 2,70	1,38 ± 2,02	0,79
4DSQ Anxiety	4,27 ± 4,66	4,27 ± 4,68	0,73
4DSQ Somatization	8,00 ± 3,35	10,04 ± 5,99	0,35

the study in the control group the intensity of symptoms decreased in 18 patients (69 %). The mean total score in the beginning of the study was 13.77, and at the end — 10.69 points (the level of mild disorder).

The effectiveness in the experimental group was greater. A decrease in the intensity of symptoms was noted in 21 patients (81 %) and the average intensity of symptoms decreased from 11.73 to 5.96 points (the borderline level). It was significantly lower than the severity of IBS and FD symptoms in the control group.

Comparison of groups in terms of "percentage improvement" also revealed a statistically significant superiority of "SZ Gastro" over placebo. If in the control group the percentage of improvement was 22.35 %, in patients in "SZ Gastro" it was 49.18 % (χ^2 = 15.9; p = 0.0001).

Evaluation of the treatment effectiveness: emotional disturbances

In the beginning of the study more than half of the patients in both groups had emotional disorders. At least one type of disorder was observed in 16 (62 %) patients in the placebo group and in 15 (58 %) patients in the experimental group. The most common disturbances in both groups in the beginning of the study were distress (54 % in the placebo group; 38 % in the SZ Gastro group) and somatization (42 % of patients in both groups).

By the end of the study, positive changes of the emotional state of patients in both groups was observed. However, in the experimental "SZ Gastro" group the improvement was greater. Thus, by the end of the study in the control group, only 42 % did not have any of the assessed emotional disorders, while in the experimental group — 73 %. The advantage of add-on "SZ Gastro" in comparison with placebo was seen in changes in severity of certain types of emotional disorders.

Approximately equal positive dynamics in both groups was noted only for depression. However, the number of patients where symptoms of distress (χ^2 = 18.7; p = 0.0000), anxiety (χ^2 = 6.9; p = 0.0097) and somatization (χ^2 = 14.99; p = 0.0001) disappeared was significantly greater in experimental group (see Table 3).

Safety

The study demonstrated a favorable safety profile of "SZ Gastro" as add-on treatment. It was well tolerated by patients and did not cause clinically significant side effects. When comparing the results of clinical and biochemical blood tests, none of the

Table 2. Comparison of the intensity of symptoms of IBS and FD in the main and control groups at baseline and during treatment

	SZ Gastro (N = 26)	**Placebo (N = 26)**	***p*-level**
7×7 "total score" in the beginning of the study	11,73 ± 4,85	13,77 ± 5,80	0,10
7×7 "total score" at the end of the study	5,96 ± 4,72	10,69 ± 7,04	0,01
% improvement*	49,18	22,35	χ^2 = 15,9 p = 0,0001

Note: * "% improvement" is calculated as the quotient of the difference between the mean at baseline and the end of the study by the average at baseline, taken as a percentage and reflects the significance of the effect obtained.

Table 3. Comparison of the effectiveness of relief of emotional disorders in the experimental and control groups

	Placebo	**SZ Gastro**	***p*-level**
Distress			
Number of patients with improvement	3 (21 %)	7 (70 %)	χ2 = 18,7; p = 0,0000
Number of patients with symptoms in the beginning of the study	14 (100 %)	10 (100 %)	
Depression			
Number of patients with improvement	6 (60 %)	7 (88 %)	χ^2 = 3,06; p = 0,08
Number of patients with symptoms in the beginning of the study	10 (100 %)	8 (100 %)	
Anxiety			
Number of patients with improvement	4 (57 %)	7 (100 %)	χ2 = 6,9; p = 0,0097
Number of patients with symptoms in the beginning of the study	7 (100 %)	7 (100 %)	
Somatization			
Number of patients with improvement	4 (36 %)	10 (91 %)	χ2 = 14,99; p = 0,0001
Number of patients with symptoms in the beginning of the study	11 (100 %)	11 (100 %)	

patients showed deviations of the studied parameters (ALT, AST, alkaline phosphatase, amylase, creatinine) from normal values.

Discussion

IBS is a difficult to treat condition, including the diversity of the etiopathogenetic mechanisms underlying this disease. Current treatment approaches, although they give a positive effect, still do not fully satisfy either patients or doctors. In this regard, the search for new options for solving the problem of treating IBS continues.

The combination of menthol, gingerol and limonene proved to be a successful way to enhance the effects of existing treatment. Ingredients included in the composition of "SZ Gastro" address the spectrum of dysfunction of organs and systems, which clinically manifests as symptoms of IBS. This activity is carried out through the regulation of motility, restoration of adequate permeability of the muco-epithelial barrier, improving the composition of the intestinal microbiota.

The add-on of "SZ Gastro" to basic treatment for a month demonstrated a significant increase in overall effectiveness, due to its positive action on the emotional state of patients: decreasing anxiety and mental stress associated with symptoms from the gastrointestinal tract. Gingerol, a component of "SZ Gastro", unlike many other plant substances, has the ability to penetrate the BBB [27]. Apparently, the consequence of this ability is its direct effect on emotional disorders, such as increased irritability, anxiety and distress symptoms, which breaks the vicious circle and in turn facilitates the management of such difficult in supervision patients.

It should be noted once more, that administration of psychopharmacological drugs to these patients requires significant efforts from the doctor: the selection of individual treatment regimens, dose titration, correction of side effects and, in most cases, observation by a psychiatrist. A general practitioner often encounters patients' distrust of psychopharmacotherapy, fear of taking such drugs. "SZ Gastro" may be a compromise solution if it is necessary to treat emotional imbalance in patients suffering from IBS and IBS in combination with FD.

Conclusion

As a result of the study, "SZ Gastro" showed its effectiveness in patients with IBS and IBS in combination with FD as an addition to standard therapy in terms of the intensity of somatic symptoms and emotional disorders. It can be assumed that it was precisely this direction of action of "SZ Gastro" that allowed him to significantly enhance the effects of well-tested in clinical trials and proven in clinical practice medicines

"SZ Gastro" was well tolerated by patients and did not cause clinically significant side effects. Relatively small sample size and relatively short follow-up period can be attributed to certain limitations of the study.

The results obtained during the study, as well as currently available data on the mechanisms of action of the active components of "SZ Gastro" allow us to conclude that the inclusion of "SZ Gastro" in the treatment regimen for patients suffering from IBS and IBS in combination with FD is clinically justified and pathogenetically justified.

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