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Lyubavskaya S.S.[1],
Chernov Y.N.[2],
Batishcheva G.A.[3],
Ushakov I.B.[4],
Goncharova N.Y.[5]

COMPLEX THERAPY OF CHRONIC PANCREATITIS COMPLICATED BY ANXIO-DEPRESSIVE DISORDERS IN RAILROAD WORKERS

1) Assistant of the Clinical Pharmacology Department, Voronezh N.N.Burdenko State Medical University, 10 Studencheskaya Street, Voronezh 394036, Russia,
2) Professor of the Clinical Pharmacology Department, Doctor of Medical Sciences, Professor, Voronezh N.N. Burdenko State Medical University, 10 Studencheskaya Street, Voronezh 394036, Russia
3) Head of the Clinical Pharmacology Department, Doctor of Medical Sciences, Professor, Voronezh N.N. Burdenko State Medical University, 10 Studencheskaya Street, Voronezh 394036, Russia, e-mail:*bat13@mail.ru*
4) Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Institute of Medico-Biological Problems, Russian Academy of Sciences, 76A Khoroshevskoye Shosse, Moscow 123007, Russia
5) Associate Professor of the Clinical Pharmacology Department, Candidate of Medical Sciences, Voronezh N.N. Burdenko State Medical University, 10 Studencheskaya Street, Voronezh 394036, Russia, e-mail: *_sumerki_@mail.ru*

Abstract. Psychic disorders in patients, who suffer from chronic somatic diseases for a long time, can be grouped into one category called psychosomatic pathology. Co-morbid – psychosomatic – disorders are considered to be predictors of unfavourable prognosis significantly aggravating patients' condition, quality of life and professional activity. It is important to timely diagnose and perform pharmacological correction of affective pathology. Special attention should be paid to patients, whose profession is associated with the operational activity. 110 railroad workers admitted to the in-patient department of the Non-state Health Care Facility "RoadHospital the Station Voronezh-1of JSC "Russian Railways" with the diagnosis "Chronic pancreatitis, recurrent" were examined in the study. On admission all patients were questioned using specialized diagnostic scales and questionnaires aimed at revealing of anxio-depressive disorders. The authors have found out negative impact of anxio-depressive disorders on the course of chronic pancreatitis with the development of stable pain syndrome, gastro-intestinal disorders, resistance to the performed pharmacotherapy, and decrease of reaction rate to presented stimuli. Examination of the patients suffering from chronic pancreatitis demonstrated that patients with MADD had more severe course of the disease. This manifested in more intensive pain syndrome, apparent symptoms of nausea, bitter taste in the mouth and diarrhea; these symptoms exceeded number of similar complaints in patients with chronic pancreatitis without MADD in 1.6 – 2.1 times. Tranquilizer "Adaptol" and anxiolytic "Afobazol" in combination with basic therapeutical medications efficiently eliminate gastroenterological and anxiety symptoms. However, "Adaptol" decreases rate of visual-motor reactions, whereas "Afobazol", on the contrary, increases reaction rate to presented stimuli.

Key words: chronic pancreatitis, anxio-depressive disorders, co-morbid pathology, psychotropic therapy, Adaptol, Afobazol, railroad workers.

Introduction. Psycho-somatic disorder is considered to be a psychogenically conditioned pathological state manifestating as an acute somatic pathology, violation of the internal body functions and physiological systems, such as the digestive, respiratory, circulatory, urinary system; this results in a specific complex of symptoms representing body reaction on the development of pathological disorders [11].

Combination of psychic and somatic violations is a characteristic feature of psycho-somatic disorders. Fundamental principle of this branch of medicine is an idea that any disease is not restricted by the clinical symptoms only (nausea, vomiting, abdominal pain, diarrhea etc.), but is manifested at several levels: emotional – a disease causes certain emotions and feelings; cognitive – comprehension of a disease; integrative – the way how an individual perceives, evaluates his condition and sees himself in the existing situation [2, 3].

The most common psychic diseases appear to be anxiety and depressive disorders; their total amount in general medical practice is approaching to 50% [3]. In practice it is very difficult to differentiate one condition from another (co-morbidity is 40 – 80%); in such cases they give evidence of mixed anxiety-depressive disorders (MADD) [5, 6, 7].

Affective disorders developing under gastrointestinal (GI) pathology are of special attention. According to various data, digestive system disorders having psychogenic origin are recorded in 30 – 70% of patients admitted to the in-patient gastroenterology departments [8, 9]. In spite of the large amount of research studies devoted to the investigation of psychosomatics in patients with GI disorders, there are comparatively few data indicating to MADD and chronic pancreatitis co-morbidity. Only a small number of works demonstrate interrelations of psychological manifestations and peculiarities of the course of pancreatic disease (severity, pain intensity, morphological changes) [110, 11, 12, 13].

Development and clinical manifestations of MADD and chronic pancreatitis are pathogenically interrelated. GABAergic and serotoninergic systems are considered to be main components of pathogenesis. Reduce of GABAergic activity provides appearance of gastroenterological panic attacks, which are manifested as discomfort in the epigastric region, nausea, rectal reflexes [14]. Serotonin appears to be an important element of gastrointestinal disorders associated with inflammation; this is connected with the violation of the innervations activity [15, 16]. When the amount of serotonin reduces, pain sensitivity increases, and even slight irritation causes apparent pain syndrome [17]. Influence of neurotransmitters on the extramural nerve endings of the gland tissue providing transmission of sensor information to the central nervous system is intensified under the inflammatory reaction. Intensification of their stimulation is associated with nauseous sensation and intestinal dysmotility [18].

Anxiety and depression aggravate the course of somatic pathology, result in delayed onset of the remission and lead to repeated hospitalizations negatively influencing professional activity [19, 20]. This fact is especially important for individuals, who work in the conditions of constant psycho-emotional stress, and psycho-traumatic (stressful) events including railroad workers (train operators, assistants of train operators, traffic controller) [21, 22].

Pharmacological correction of combined pathology containing neurotic disorders is sufficiently complicated, especially in individuals working as operators [23]. Pharmaceutical effect on the professional abilities of train drivers is considered to be the issue of the day all over the world [24]. More than ten countries (Germany, France, Spain and others) have lists of drug products with indication of their danger level that is specified depending on their effect on the central nervous system when being taken by vehicle operators [25].

"Classification of drug products depending on the level of their negative effects on the professionally significant functions of train operators and other operators' professions" developed by Tsfasman A.Z. et al. [23] in 2011 is currently a must in the Russian Federation when administering drug therapy for railroad workers.

Thus, timely diagnostics, effective and safe MADD and chronic pancreatitis pathogenetic therapy are very important for the treatment of railroad workers.

Materials and methods. The research study was made on the basis of the Clinical Pharmacology Department of the Voronezh N.N. Burdenko Medical University and Gastroenterology Department of the Non-state Health Care Facility "Road Hospital the Station Voronezh-1of JSC "Russian Railways".

110 railroad workers admitted to the in-patient department with the diagnosis "Chronic pancreatitis, recurrent" (section K86.1 "Other chronic pancreatitis" of the International Classification of Diseases, 10th edition) were examine in the study. Among them there were 78 males and 32 females, average age 44.5±2.8, including 42 assistants of the train operators (38.2%), 29 train operators (26.4%), 20 train hosts (18.2%) and 19 train traffic controllers (17.2%); 24 healthy railroad workers, average age 42.4±1.7, formed a separate study group.

On admission all patients were questioned using specialized diagnostic scales and questionnaires aimed at revealing anxio-depressive disorders. These questionnaires included Hospital Anxiety and Depression Scale HADS (anxiety/ depression), Zung Anxiety Rating Scale ZARS (self-evaluation of depression), Spielberger-Khanin test (personal and reactive anxiety), a questionnaire "Health, Activity, Mood" (*CAH in Russian*). The diagnose "Mixed anxiety and depressive disorder" was made according to the International Classification of Diseases, 10th edition (section F41.2 "Mixed anxiety and depressive disorder").

Modified graduated Visual Analogue Scale (VAS) was used to evaluate intensity of pain syndrome and gastroenterological symptoms; intensity of pain syndrome and dyspeptic disorders (nausea, bitter taste in the mouth, diarrhea) were assessed according to a 5-point system.

Activity of the inflammatory process of the pancreas was defined on the level of serum amylase, pancreatic amylase and lipase in the biochemical blood assay. Ultrasound examination of the pancreas was performed to specify its sizes, boundaries, structure and parenchymal echo-genicity.

Assessment of psycho-physiological functional status was performed using psycho-diagnostic complex "Select-M" *(«Селект-М» in Russian*). Participants were tested in an isolated, sound proof,

darkened room. Intensity and lability of nerve processes were investigated by defining a simple motor response (m/sec) to the red signal, complex motor responses to green light and to red light taking into account decision-making time. To differentiate psycho-motor or motor inhibition critical frequency of fusion flicker (CFFF) test was performed. The reaction to a moving object including an average passing time value, an average response time out value was used to estimate balance between excitation and inhibition processes in the cerebral cortex. Study results were interpreted according to "Methodological instructions on performing psycho-physiological examinations in the railway locomotive facilities" (№ 310y, Ministry of Railways of the Russian Federation, December 1, 1999) [26].

Pharmaco-economic analysis was performed using software application "Calculation of the individual treatment cost" (certificate of registration №2011610459, January 11, 2012) [27].

Statistical data were processed using software application "SPSS 9.0"; the mean value (X) of standard deviation was estimated by calculating a mean error of the arithmetical mean value (m). Non-parametric Wilcoxon signed-rank test was used to estimate confidence rating. Correlation dependence was determined according to Spearman method.

Results. Comparative analysis of two groups of patients was performed **at the first stage** of study to assess MADD influence on the course of chronic pancreatitis and psycho-physiological functions: patients with chronic pancreatitis (n=45) and patients suffering from chronic pancreatitis and MADD (n=65). The control group consisted of healthy railway workers (n=24); the rate of visual-motor reactions was the only parameter determined in this group.

The analysis of the results according to psycho-diagnostic scales giving an opportunity to diagnoseanxio-depressive disorders has demonstrated that anxiety and depression level in patients with chronic pancreatitis and MADD on HADS (anxiety/ depression) and Zung (depression) scales exceeds similar findings in the group of patients with chronic pancreatitis without affective disordersin 1.9 – 2.6 times ($p< 0.01$), and normative values in 1.3 – 2 times (Table 1).

Table 1.

Findings of psycho-diagnostic examination (X±m).

Findings	Normative values	Patients with chronic pancreatitis (n=45)	Patients with chronic pancreatitis and MADD (n=65)
HADS Scale			
HADS, anxiety, points	≤7	5,4±1,2	13,9±1,7**
HADS, depression, points	≤7	3,8±0,9	9,2±2,1**
Zung Scale			
Depression, points	<50	34,1±1,7	63,9±2,1**
Spielberger – Khanin test			
Personal anxiety,points	≤30	41,5±1,2	58,3±2,9**
Reactive anxiety, points	≤30	30,5±2,6	59,1±2,2**
Health, Activity, Mood test			
Health, points	≥5	4,2±0,3	2,2±0,5**
Activity, points	≥5	5,3±0,2	3,3±0,7**
Mood, points	≥5	4,4±0,7	3,1±0,3*

Note: * - $p<0.01$ – confidence rating with the results of patients suffering from chronic pancreatitis.

Study of psycho-emotional sphere according to Spielberger-Khanin test has revealed an increased level of reactive and personal anxiety in 29 patients (64.4%) with chronic pancreatitis and in all patients (100%) with combined chronic pancreatitis and MADD pathology, maximally expressed in patients with co-morbid pathology. Alongside with the high level of anxiety a significant decrease of findings on the "Health, Activity, Mood" test was recorded in patients suffering from affective disorders; this fact gives evidence of negative self-evaluation (Table 1).

Concerning somatic disorders all the examined patients complained of pain syndrome and dyspeptic disorders (nausea, bitter taste in the mouth, diarrhea). However, intensity of gastroenterological symptoms was different in the comparable groups. In patients with chronic pancreatitis having no any signs of anxiety and depression pain according to VAS Scale was moderate averaging 2.8±0.1 points ("a symptom is slightly revealed", "a symptom is moderately revealed"), whereas patients with chronic pancreatitis and MADD evaluated intensity of stomach-ache of

psychogenic nature as 4.5±0.6 points ("a symptom is severely revealed", "a symptom is very severely revealed"). Findings "nausea, bitter taste in the mouth, altered defecation pattern" in patients with combined pathology exceeded similar findings in patients suffering only from chronic pancreatitis in 1.6 – 2.1 times (Table 2).

Table 2.

Gastroenterological findings according to VAS Scale (X±m).

Findings	Patients with chronic pancreatitis (n=45)	Patients with chronic pancreatitis+MADD (n=65)
Pain syndrome, points	2,8±0,1	4,5±0,6*
Nausea, points	2,3±0,2	4,9±0,8**
Bitter taste in the mouth, points	2,1±0,5	3,6 ±0,3*
Altered defecation pattern (diarrhea), points	1,6±0,1	3,5±0,2**

Note: * - p<0.05, ** - p<0.01 – confidence rating with the results of patients suffering from chronic pancreatitis.

According to the results of biochemical blood assay estimating enzymatic status changes of serum amylase level, pancreatic amylase level and blood lipase were registered in 22 patients (33.8%) with chronic pancreatitis and MADD. Thus, the value of serum amylase was 124.5±2.9 U/l, level of pancreatic amylase achieved upper limit of normal being less than 54.4±3.2 U/l, blood lipase averaged 67.3±1.9 U/l. The results obtained exceeded normal values in 1.2 times.

In contrast to patients with neurotic disorders, elevated enzyme level was revealed in 34 testees (75.5%) of the group of patients with chronic pancreatitis and without MADD; that was by 55.2% more often comparing to patients with MADD. Serum amylase level amounted 206.7±4.7 U/l, pancreatic amylase level amounted 93,2±3,3 U/l, blood lipase level amounted 94,7±2,8 U/l; this exceeded normal values in 1.6 – 2 times and similar values in the group of patients with combined chronic pancreatitis and MADD in 1.4 – 1.7 times (p<0,05; p<0,05; p<0,01).

According to ultrasound (US) examination of the pancreas diffuse changes of the organ tissue were revealed in all patients: irregular indistinct boundaries, elevation of echogenicity, inhomogeneity of parenchyma. However, increased sizes of a gland were observed in 73.3% of patients with chronic pancreatitis and in 20% of patients with chronic pancreatitis and MADD only.

The obtained clinico-laboratory and instrumental data in the group of patients with chronic pancreatitis gave explanation to presence of gastroenterological complaints and supported principal diagnosis; whereas in the group of patients with combined pathology clinical findings to a greater extent indicated at presence of psycho-somatic disorders.

Evaluation of psycho-physiological functions in patients with chronic pancreatitis and without MADD demonstrated average values of visual-motor reactions rate; this fact indicated at the stability of processes of psycho-motor reactions and was comparable to the test performance rate in the group of healthy railroad workers (Table 3).

Table 3.

Findings of psycho-physiological functions prior to initiating therapy(X±m).

Findings	Control group (n=24)	Patients with chronic pancreatitis (n=45)	Patients with chronic pancreatitis and MADD (n=65)
Simple motor response, m/sec	351,3±18,9	350,8±12,3	510,3±10,4*
CFFF, Hz	37,8±4,3	34,5±5,9	35,6±4,7
Complex motor response to red light, m/sec	419±16,8	508,2±10,6	626,9±8,8*
Complex motor response to green light, m/sec	461±21,6	452,5±19,5	685,3±17,1**
Decision-making time$_{red}$	115,4±22,8	135,6±19,6	179,5±18,3*
Decision making time$_{green}$	95,7±19,9	131,9±21,5	156,3±14,3
Reaction to a moving object including an average passing time value, m/sec	46,9±4,5	48,9±5,7	47,2±8,3
Reaction to a moving object including an average response time out value, m/sec	48,3±4,4	58,9±5,2	116,3±11,4**

Note: * - p<0.05, ** - p<0.01 – confidence rating with the results of patients suffering from chronic pancreatitis.

In the group of patients with co-morbid pathology aggravation of test results with manifestations of inhibiting reaction was registered in78.4% of cases. Investigation of simple motor response demonstrated increased time of task performance by 45.5% (p<0.05) comparing to the result of test performance rate in the group of patients without anxiety and depression. The amount of CFFF

at that was 35.6±4.7 Hz, which is considered to be an average value and against the background of low simple motor response values is interpreted as the decrease of psycho-motor reaction. Test performance time in case of complex motor response to red and green light, as well as decision-making time to red light was respectively by 23.3%, 51.4% and 32.3% low than in patients with chronic pancreatitis ($p<0,05$, $p<0,01$; $p<0,05$). When performing the reaction to a moving object test in patients with chronic pancreatitis and MADD, the response time out reaction to a presented stimulus was prevalent. Average response time out values of the reaction to a moving object were 2 times higher in the group of patients without MADD ($p<0,01$) (Table 3).

The following observation groups were formed out at **the second stage** of research study considering character of the conducted therapy: the control group (n=45) – patients with chronic pancreatitis (principal disease) without signs of anxiety and depression receiving standard (basic) pharmacotherapy (enzymatic preparations, proton pump inhibitors, spasmolytic drugs, non-narcotic analgetics, antidiarrheal preparations); the 1st group (n=25) – patients with combined chronic pancreatitis and MADD receiving only basic therapy against their principal disease; the 2nd group (n=20) patients with combined chronic pancreatitis and MADD receiving tranquilizer of nonbenzodiazepine series – Tetramethyltetraazabicyclooctandione ("Adaptol") in addition to basic preparations; the medication was given in a daily dose 1000 mg divided into 2 intakes (500 mg twice a day) independently on a meal; the 3rd group of testees (n=20) was patients with chronic pancreatitis and MADD simultaneously taking basic preparations and selective anxiolytic Fabomotizole ("Afobazol") in daily dose 30 mg divided into 3 intakes (10 mg three times a day) after meal.

After being discharged from the hospital all testees continued taking enzymatic preparations and proton pump inhibitors out-patiently for 14 days. Psychotropic therapy was being performed up to 30 days.

The effectiveness and safety of treatment was evaluated on the 7th, 14th and 30th days of the treatment onset. Unfavourable side effects were being monitored during the whole period of observation for patients.

Significant decrease of the anxiety component was registered according to the HADS Scale against the background of psychotropic drugs administration. Anxiety value in the 2nd group of patients taking "Adaptol" decreased from 13.6±1,8 to 10,8±0,7 points ($p<0,05$) on the 7th day of the therapy, to 8,9±0,4 points ($p<0,05$) on the 14th day of the therapy, to 7,8±0,8 points ($p<0,01$) on the 30th day of examination. In the 3rd group of patients taking "Afobazol" anxiety level also reduced from 13.9±2,1 to 10,2±0,6 points ($p<0,05$) on the 7th day of the therapy, to 9,3±1,2 points ($p<0,01$) in two weeks after administering the preparation, to 7,9±0,8 points ($p<0,01$) on the 30th day of the therapy (Figure 1).

In contrast to patients, who were given pharmacological correction of MADD, anxiety level in the 1st group of patients receiving only basic preparations was not significantly altered: 14±2,2 points before treatment, 13,3±2,6 points on the 7th day of the therapy, 13,6±3,1 points on the 14th day, 13,8±1,4 points on the 30th day; this exceeded upper normal limits in 1.9 times (Figure 1).

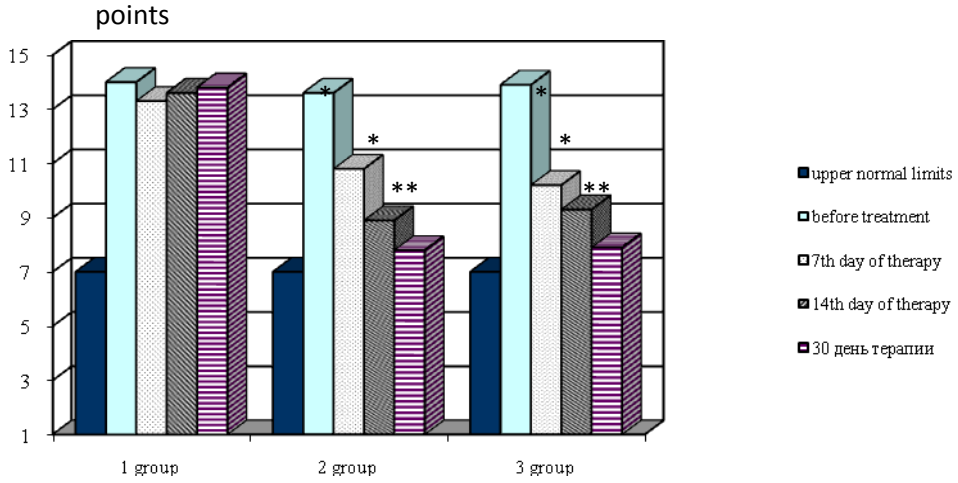

Figure 1. Dynamics of the anxiety level according to the HADS Scale against the background of the complex therapy.
Note: * - $p<0,05$, ** - $p<0,01$- confidence rating with the results of examination before the treatment onset.

Control of the depression level according to the HADS and Zung Scales on the 7th and 14th day of the therapy did not reveal significant dynamics of the indicated value in both - patients receiving anxiolytics ("Adaptol", "Afobazol") and patients, who were administered only basic therapy of chronic pancreatitis. The depression value according to HADS and Zung Scales in the 1st group of patients was at the same level on the 30th day of examination, whereas it had a statistically non-significant tendency to reduce in the 2nd and 3rd groups.

According to Spielberger-Khanin test the reactive anxiety value in the control group was 28,6±2,2 points against the background of the basic therapy on the 14th day of treatment; the obtained values were the same on the 30th day of examination. Personal anxiety level had no changes during the whole course of the therapy being 37,5±2,1 points on the 7th day of treatment, 42,6±2,8 points on the 14th day and 38,6±3,2 points on the 30th day. Results demonstrated low level of reactive anxiety and moderate level of personal anxiety (Table 4).

Table 4.

Dynamics of the anxiety values according to Spielberger-Khanin test against the background of pharmacotherapy (X±m).

Value	Before treatment	7th day of treatment	14th day of treatment	30th day of treatment
Control group (n=45)				
Personal anxiety, points	41,5±1,2	37,5±2,1	42,6±2,8	38,6±3,2
Reactive anxiety, points	30,5±2,6	32,6±3,5	28,6±2,2	28,3±2,9
1st group (n=25)				
Personal anxiety, points	61,3±2,1	58,7±1,8	53,5±1,9	65,8±3,6
Reactive anxiety, points	56,7±0,9	52,3±0,5	53,6±1,2	54,2±2,8
2nd group (n=20)				
Personal anxiety, points	59,7±1,9	55,2±2,4	44,1±2,2*	45,6±1,9*
Reactive anxiety, points	60,2±1,2	54,3±2,4	48,3±1,6*	42,6±1,6*
3rd group (n=20)				
Personal anxiety, points	63,2±2,2	58,2±1,7	48,7±2,4*	47,8±2,1*
Reactive anxiety, points	56,5±1,2	49,7±2,7	37,4±4,2**	32,4±3,5**

Note: * - p<0,05, ** - p<0,01- confidence rating with the results of examination before the treatment onset.

In the 1st group of patients with co-morbid pathology, who were given therapy only for chronic pancreatitis, values of personal and reactive anxiety during the whole period of in-patients and out-patients treatment were at the same level as before treatment being more than 46 points (high level of anxiety).

A significant decrease of anxiety values was registered on the 14th day of the therapy against the background of "Adaptol" and "Afobazol" administration. On the 30th day of examination personal and reactive anxiety values in patients of the 2nd group receiving "Adaptol" were at the obtained level being less than 46 points (moderate anxiety). In contrast to the 2nd group of patients intensity of reactive anxiety significantly reduced in patients of the 3rd group taking "Afobazol" – by 42.6% comparing to the initial level and obtained 32,4±3,5 points (< 30 points is considered to be low level of anxiety).

According to the results of "Health, Activity, Mood" test health and mood findings in patients of the control group tended to increase amounting to 5,8±0,2 points (p<0,05) and 5,4±0,2 points respectively (p<0,05) on the 14th day of treatment. Activity findings were at the sufficiently high level of 5,5±0,2 points as before treatment. On the 30th day of examination health, activity, mood findings were within normal limits (more than 5 points) (Table 5).

In the 1st group of patients with chronic pancreatitis and MADD, who were given only standard pharmacotherapy, there were no significant improvements on the 7th, 14th and 30th days according to "Health, Activity, Mood" test. Health, activity and mood values in patients were at the same low level as before treatment being no more than 3.4 ±0.5 points.

Positive self-evaluative dynamics of the patients' condition according to "Health, Activity, Mood" test was recorded in the 2nd and 3rd group of patients with combined pathology taking tranquilizers alongside with basic preparations in 2 weeks of pharmacotherapy. Thus, health and mood values increased by 78.8% and 30.5% respectively (p<0.01, p<0.05) on the 14th day of treatment obtaining 5 and more points score on the 30th day of treatment. Activity level at that was low during the whole period of study. Opposed to "Adaptol", "Afobazol" had a positive impact not only on the health and mood, but also on the activity level. All findings tended to increase by 73.9%, 37.5 % and 53.3% respectively (p<0,05, p<0,01) on the 14th day of treatment obtaining more than 5 points score on the 30th day of examination.

Table 5.

Results of psychological test according to "Health, Activity, Mood" questionnaire against the background of pharmacotherapy (X±m).

Value	Before treatment	7th day of the therapy	14th day of the therapy	30th day of the therapy
Control group (n=45)				
Health, points	4,2±0,3	4,8±0,1	5,8±0,2*	5,6±0,2
Activity, points	5,3±0,2	5,2±0,5	5,5±0,2	5,3±0,3
Mood, points	4,4±0,7	4,6±0,2	5,4±0,4*	5,4±0,2*
1st group (n=25)				
Health, points	2,5±0,7	2,9±0,3	3,2±0,6	2,7±0,3
Activity, points	3,5±0,3	3,1±0,5	3,4±0,5	2,9±0,2
Mood, points	2,9±0,1	2,2±0,2	2,5±0,2	3,4±0,2
2nd group (n=20)				
Health, points	1,9±0,5	2,8±0,3	3,4±2,2**	5±0,3**
Activity, points	3,1±0,3	3,3±0,2	2,9±0,4	3,7±0,5
Mood, points	3,6±0,2	4,2±0,2	4,7±0,4*	5,2±0,3**
3rd group (n=20)				
Health, points	2,3±0,5	3,9±0,2	4±0,2**	5,4±0,6**
Activity, points	3,2±0,2	3,5±0,5	4,4±0,3*	5,2±0,2**
Mood, points	3±0,2	4,2±0,1	4,6±0,2*	5,2±0,2**

Note: * - p<0,05, ** - p<0,01- confidence rating with the results of examination before the treatment onset.

According to VAS reduction of pain syndrome from 2,8±0,1 points to 1,6±0,1 points (p<0,01) was registered in the group of patients with chronic pancreatitis and without MADD on the 7th day of pharmacotherapy with the followed positive dynamics on the 14th day of therapy when pain intensity in 86.8% of patients amounted to 1 point (p<0,01); that indicated at the "lack of symptom". On further examination 93.3% of patients reported the pain intensity being equal to1 point (p<0,01) when completing VAS questionnaire in 30 days after the treatment onset. On the contrary, no positive dynamics was observed on the value "stomach-ache of psycho-genic nature" in patients of the 1st group with combined pathology on the 7th, 14th and 30th days of the therapy. In the 2nd group of patients taking "Adaptol" pain intensity level decreased from 3,9±0,2 to 2,5±0,6 points (p<0,05) on the 14th day and to 1,8±0,2 points (p<0,01) on the 30th day of the therapy. In the 3rd group of patients receiving "Afobazol" a significant decrease of pain syndrome from 4,3±0,1 to 2,7±0,8 points (p<0,05) was registered as early as on the 7th day of the therapy with the followed tendency to reduce up to 1,5±0,1 points (p<0,01) on the 14th day of examination; that was comparable with the results of treatment in patients of the control group with chronic pancreatitis. On the 30th day of examination the value "stomach-ache of psycho-genic nature" remained at the obtained level - 1,5±0,2 points (p<0,01) (Figure 2).

Evaluation of dynamics of other gastroenterological symptoms in patients of the control group revealed gradual decrease of nausea intensity, bitter taste in the mouth and diarrhea. On the 7th day of treatment nausea intensity decreased from 2,3±0,2 to 1,9±0,6 points (p<0.05), bitter taste in the mouth – from 2,1±0,5 points to 1,7±0,4 and diarrhea – from 1,6±0,1 points to 1,3±0,3 points. On the 14th day of treatment of chronic pancreatitis exacerbation the above-mentioned values in 87.7% of patients did not exceed 1 point score (p<0,01; p<0,01; p<0,05), that indicated at the lack of gastroenterological manifestations. On the 30th day of the therapy no patients complained of gastrointestinal disorders.

Patients of the 1st group reported about dyspeptic disorders at the same level as before the treatment onset comparing to patients of the control group. During the whole course of treatment severity of nausea, bitter taste in the mouth and diarrhea were equal to 3 – 4 points; this indicated at the "moderately revealed" and "severely revealed" symptoms. Diarrhea status decreased by 23.7% (p<0.05) on the 30th day of the therapyonly.

When performing complex treatment with application of psychotropic preparation severity of dyspeptic disorders also tended to decrease. In patients of the 2nd group, who received "Adaptol" alongside with the basic therapy, somatic findings improved on the 14th day of treatment – nausea severity decreased from 4,7±0,2 to 2,5±0,9 points (p<0.01), diarrhea severity decreased from 3,9±0,2 to

2,4±0,5 points (p<0.05); complaints on the bitter taste in the mouth remained unchanged, its intensity level amounted 3,2±0,9 points as before treatment. On the 30th day of treatment severity level of nausea and diarrhea amounted 1-2 points (p<0,01), this indicated at the "slightly revealed symptom". Severity of nausea and diarrhea at that amounted 1 point ("lack of symptom") in 45% of patients. Severity of the bitter taste in the mouth was without essential dynamics - 2,9±0,4 points. In contrast to "Adaptol" intake "Afobazol" administration allowed receiving therapeutical results as early as the 7th day of treatment; this was manifested in significant decrease of complaints on nausea from 4,6±0,2 to 3,4±1,2 points (p<0,05), bitter taste in the mouth - from 4,05±0,7 to 3,2±0,3 points (p<0,05); severity of diarrhea tended to decrease from 3,8±0,2 to 3,2±0,3 points. On the 14th day of treatment the above-mentioned symptoms did not exceed 2.6±0.2 points; on the 30th day of examination 55% of patients did not complain of nausea, bitter taste in the mouth and diarrhea (Figure 2).

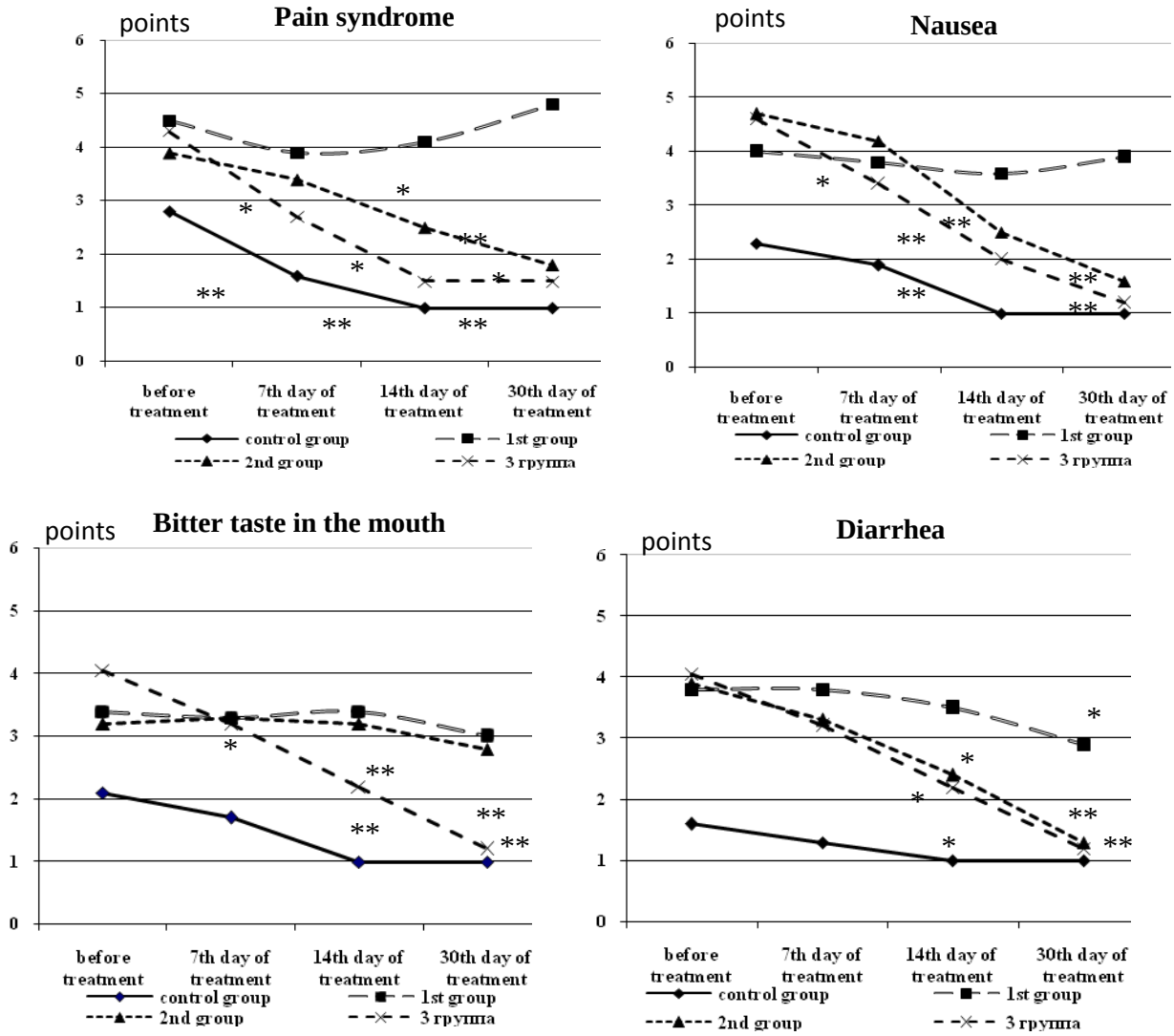

Figure 2. Dynamics of gastroenterological symptoms against the background of the therapy.
Note: * - p<0,05, ** - p<0,01- confidence rating with the results of examination before the treatment onset.

Control of biochemical findings against the background of the performed treatment demonstrated favourable effect of basic and complex therapy on the enzymatic status; this was manifested by the significant decrease of serum amylase, pancreatic amylase and blood lipase level.

Analysis of the rate of visual-motor reactions in the group of patients with chronic pancreatitis having no MADD (the control group), who received basic preparations, showed that there were no negative changes in the rate of visual-motor reactions; this indicated at the safety administration of preparations applied for the treatment of chronic pancreatitis in the context of professional operational activity.

The rate of visual-motor reactions in patients with chronic pancreatitis and MADD, who received

only basic preparations (the 1st group) was not altered during the whole course of in-patient and out-patient treatment. Rate of a simple motor response, a complex motor response, a reaction to a moving object was low with prevailing processes of inhibition and decrease of psycho-motor reaction.

In the 2nd group of patients, who were additionally administered "Adaptol", test performance time of a simple motor response increased by 32% comparing to the initial level ($p<0.05$) on the 14th day of treatment; decision-making time (to green light) tended to increase by 27% comparing to the given parameter on the 14th day of examination ($p<0.05$). The results obtained were interpreted as the tendency to slow the rate of visual-motor reactions (Table 6).

Table 6.

Findings of psycho-physiological functions in patients with chronic pancreatitis and MADD against the background of complex therapy including "Adaptol"(X±m).

Findings	Before treatment	7th day of treatment	14th day of treatment	30th day of treatment
Simple motor response, m/sec	465,2±8,7	478,3±12,9	615,7±11,5*	614,2±12,9*
CFFF, Hz	33,6±2,5	38,9±4,7	36,6±7,2	34,3±2,9
Complex motor response to green light, m/sec	698,1±11,4	697,5±15,8	679,3±13,9	665,4±16,7
Complex motor response to green light, m/sec	701,5±17,3	679,5±12,1	686,4±10,4	698,7±11,8
Decision-making time$_{green}$	156,4±15,6	147,2±15,6	158,3±12,5	198,7±16,8#
Decision-making time$_{red}$	176,4±12,4	167,3±18,2	166,9±22,6	169,7±15,8
Average passing time, m/sec	50,1±4,9	44,6±5,2	58,7±7,2	47,3±5,7
Average response time out value, m/sec	110,2±9,6	114,3±8,3	117,3±4,6	112,6±6,6

Note: * - $p<0,05$ - confidence rating with the results of examination before the treatment onset;
-$p<0,05$ $p<0,05$ - confidence rating with the results of examination on the 14th day of treatment.

In contrast to "Adaptol" intake administration of "Afobazol" reduced task performance time: performance time of a simple motor response decreased by 22.8% on the 7th day of therapy ($p<0.05$); performance time of a complex motor response to green light decreased by 30.2% ($p<0.05$), to red light – by 25.4% ($p<0.05$) on the 14th day of treatment; a reaction to a moving object including average response time out value decreased by 19.5%, a reaction to a moving object including average passing time value remained unchanged. In 2 weeks of anxiolytic "Afobazol" intake psycho-physiological findings reached average values of reaction to the presented stimulus typical for patients without MADD. On the 30th day of treatment performance time of a simple motor response, CFFF, a complex motor response, a reaction to a moving object reached normative values conforming with the average reaction time to a signal (Table 7).

Table 7.

Findings of psycho-physiological functions in patients with chronic pancreatitis and MADD against the background of complex therapy including "Afobazol"(X±m).

Findings	Before treatment	7th day of treatment	14th day of treatment	30th day of treatment
Simple motor response, m/sec	472,5±12,9	364,3±9,2*	325,8±8,9	337,7±10,3
CFFF, Hz	38,8±2,9	40,6±4,8	39,7±6,9	37,4±7,5
Complex motor response to green light, m/sec	718,2±12,2	686,9±13,9	501,5±7,7*	513,7±8,9*
Complex motor response to green light, m/sec	689,2±10,2	702,3±8,4	513,9±7,2*	527,5±9,8*
Decision-making time$_{green}$	158,3±13,6	164,6±6,6	139,2±15,4	146,7±13,9
Decision-making time$_{red}$	184,7±15,8	179,5±14,7	149,2±15,4	156,7±13,9
Average passing time, m/sec	44,2±8,3	45,6±7,3	51,7±3,9	43,8±5,9
Average response time out value, m/sec	114,6±5,9	97,2±8,8	92,3±5,9*	94,3±7,8*

Note: * - $p<0,05$, ** - $p<0,01$- confidence rating with the results of examination before the treatment onset.

At the third stage of study pharmaco-economic analysis was performed**.** For this all the patients were divided into 4 groups: the 1st group (n=45) – patients with chronic pancreatitis, who received standard therapy for the principal disease; the 2nd group (n=25) – patients with chronic pancreatitis and MADD, who were administered only basic preparation; the 3rd group (n=20) – patients with chronic pancreatitis and MADD, who received anxiolytic "Adaptol" alongside with the standard treatment; the 4th group (n=20) – patients with chronic pancreatitis and MADD, who were administered basic preparations and anxiolytic "Afobazol".

Performed pharmaco-economic analysis showed that treatment cost with gastroenterological preparations in the 2nd group of patients with the combine pathology, who were not administered MADD correction, exceeded treatment cost of patients without affective pathology in 2 times ($p<0.01$) and in the group of patients receiving psychotropic medications "Adaptol" or "Afobazol" in 1.6 and 1.5 times respectively ($p<0.05$) (cost of these medications was not taken into account) (Figure 3).

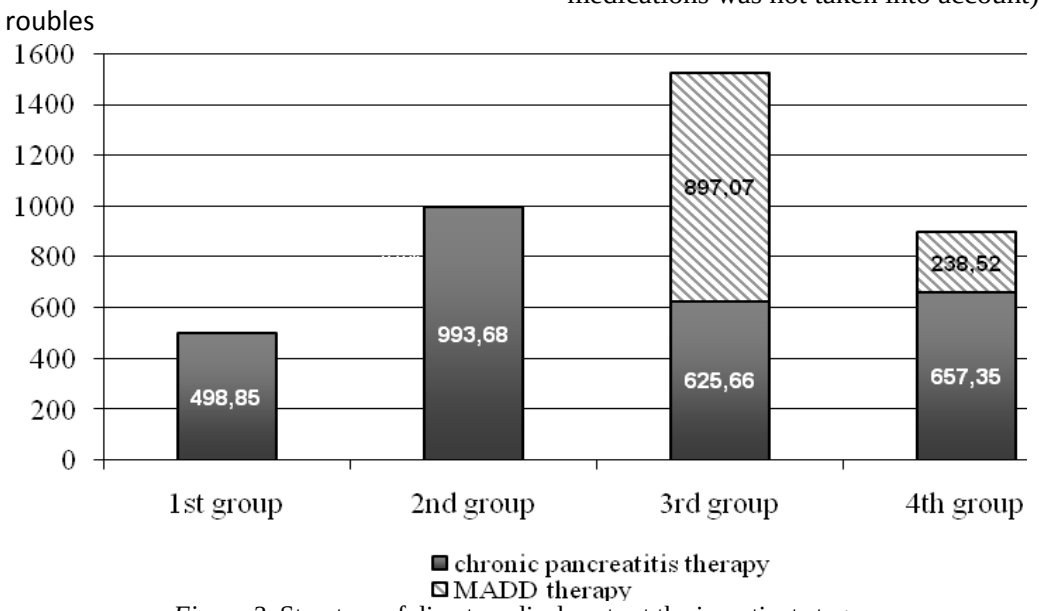

Figure 3. Structure of direct medical costs at the in-patient stage.
Note: ## - $p<0,01$ – confidence rating of patients without MADD; * - $p<0,05$- confidence rating of patients receiving psychotropic preparations.

Administration of psychotropic therapy to patients with MADD reduced spasmolytics intake by 24.1%, analgesics intake by 23.9% and prokinetics intake by 28.5% in average, due to the effective elimination of the pain syndrome and dyspeptic disorders, since their intensity, as it was shown in the study, was related to the affective disorders. As a result, the therapy course with indicated preparations in patients with chronic pancreatitis and MADD receiving psycho-pharmacotherapy was practically approaching to the course dose of preparation intake in patients with chronic pancreatitis without signs of anxiety and depression, and therapeutical costs were consequently lower (Table 8).

Table 8.

Treatment of chronic pancreatitis with basic preparations.

Group	Spasmolytic, days	Analgesics, days	Prokinetics, days
1st group (n=45)	7,2±0,2	5,3±0,2	5,4±0,3
2nd group (n=25)	10,6±1,8	9,2±1,1	8,4±1,2
3rd group (n=20)	7,9±1,3	7,2±0,4	5,8±1,2
4th group (n=20)	8,2±1,4	6,8±1,5	6,2±1,4

Complex therapy cost estimation considering cost of psychotropic preparations showed that "Adaptol" administration increased chronic pancreatitis and MADD treatment costs by 58.9%, whereas additional intake of "Afobazol" did not cause any significant price elevation, expenses at that rose by 26.6%.

When evaluating an individual tolerability of administered psychotropic preparations, patients were interviewed to reveal adverse drug reaction (ADR)

typical for medications of tranquilizers group (sleepiness during the daytime, muscle relaxation and drug addiction), as well as side effects described in the instruction for medical use of "Adaptol" (dizziness, decrease of blood pressure, fatigue, dyspeptic disorders, allergic reactions) and "Afobazol" (allergic reactions, headache).

No unfavourable effects or apparent health deterioration demanding cancellation of preparation or daily dose decrease were registered during the observation against the background of "Adaptol" and "Afobazol" therapy.

When analyzing an individual tolerability of "Adaptol" 70% of patients complained of the apparent bitter taste in the mouth appearing right after the preparation intake and occurring during the whole therapy course. Besides, 55% of patients spoke about inconvenience of taking the preparation, which was related to the large size of a tablet. One patient noted intensification of dizziness during the first 10 days of "Adaptol" therapy. However, no significant changes of blood pressure and pulse rate were registered at the checkups.

10% of patients in the group of patients receiving "Afobazol" had sleeping disorders in the form of sleepiness during the daytime, which appeared on the 3-4 day of the treatment onset and compensated spontaneously on the 5-7 day of treatment. One patient, who was emotionally excited about his psycho-somatic status even before the psycho-pharmacorrection therapy onset, revealed prevalence of depressive component in the psychological testing, his reactive and personal anxiety was of high level; after the treatment course he reported about the development of "withdrawal symptoms" and, as a result, drug addiction to "Afobazol". 30% of patients did not agree with the frequent daily intake of the preparation (3 times a day), but they followed therapy regimen and fully completed it.

Discussion. Examination of the patients suffering from chronic pancreatitis demonstrated that patients with MADD had more severe course of the disease. This manifested by intensive pain syndrome, apparent symptoms of nausea, bitter taste in the mouth and diarrhea exceeding similar complaints in patients with chronic pancreatitis having no any sign of anxiety and depression in 1.6-2.1 times.

The fact that in75.5% of patients with chronic pancreatitis without MADD biochemical findings (serum amylase, pancreatic amylase, blood lipase) exceeded normative values in 2 times and US examination of the pancreas revealed its enlargement was of great significance. In contrast to patients without signs of anxiety and depression elevated level of enzymes was registered only in 38.8% of patients with combined pathology exceeding upper normative limits in 1.2 times, and US examination results indicated at the alteration of gland tissue without altering its sizes. The obtained data conform to research studies performed earlier, which demonstrated that it is impossible to reveal objective and significant gastro-intestinal changes in somatic patients with neurotic disorders during thorough repeated laboratory and instrumental investigations [28].

Psychodiagnostic test results in patients with co-morbid pathology revealed prevalence of the anxiety level that was 2 times higher than normative values according to HADS and Zung Scales. Survey results demonstrated that more than half a number of all patients were under conditions of constant stress for a long period of time (3 – 7 years). They reported about severe labour environment, shift basis working hours including night shifts, feeling of excessive responsibility at their working place. This supports the fact of developing anxio-depressive disorders mostly in patients, whose professional activity is subjected to long-lasting psycho-emotional overstrain [29, 30].

According to test results 100% of patients with co-morbid pathology revealed elevated level of reactive and personal anxiety with the intensity of 58,3±2,9 and 59,1±2,2 points (46 points and more indicate at the high level of anxiety). The data obtained support the fact that elevation of situational and personal anxiety in locomotive crew workers increases risk of developing pathological somato-vegetative violations that cause inner organ disorders and deterioration of psycho-physiological functions [31].

Assessment of combine pathology impact on the rate of visual-motor reactions appears to be an important aspect of study. The obtained results estimate presence of inhibiting reaction in 78.4% of patients. For example, rate of simple motor response was decreased in 45.5% comparing to the analogue reaction in patients without MADD ($p<0.05$). CFFF at that was in the range of average values and in the context of low simple motor response values was interpreted as decrease of psycho-motor reaction (according to "Methodological instructions on performing psycho-physiological examinations in the railway locomotive facilities" № 310y, Ministry of Railways of the Russian Federation, December 1, 1999). Test performance time for a complex motor response to green and red light was by 23.3% and 51.4% more than in patients with chronic pancreatitis without affective pathology ($p<0.01$, $p<0.05$). According to results of the reaction to a moving object test average response time out values exceeded normative values amounting 116.7±11.4 m/sec ($p<0.01$) with normative values of an average passing time – 47.2±8.3 m/sec.

As a psychotropic therapy preparations patients were administered non-benzodiazepine tranquilizer Tetramethyltetraazabicyclooctandione ("Adaptol") in a daily dose 1000 mg and selective non-benzodiazepine anxiolytic Fabomotizole ("Afobazol") in a daily dose 30 mg. Administration of the given preparations is pathogenically proved, since their action is aimed at the strengthening of GABAergic and serotoninergic mechanisms in the brain [32, 33].

Impact of preparations on the rate of visual-motor reactions revealed during the research study appeared to be a restriction to apply "Adaptol" in train operators, assistants of train operators, traffic controllers at the out-patient stage of treatment. Only train hosts continued receiving this preparation after being discharged from the hospital. In 2011 "Adaptol" was included in the list of the 1st class preparations that are considered to be dangerous for the on-the-job administration for train operators and their assistants, since it can result in hypertension, fatigue and dizziness (study guidelines, IVth edition, updated and revised, "Medications and safety of train traffic" by Professor Tsfasman et al., 2011). Changes indicating at the "Adaptol" potential to negatively influence the ability to drive transport vehicle and serve mechanisms causing possible decrease of blood pressure and fatigue were included in the Instruction for medical use of preparation (2011) [34].

Observation results of patients suffering from chronic pancreatitis and MADD demonstrate that clinical use of preparations of the non-benzodiazepine tranquilizer group "Adaptol" and "Afobazol" as a part of complex therapy allows conducting effective pharmacotherapy with favourable impact on gastrointestinal and anxiety symptoms.

In the context of "Adaptol" administration the level of pain syndrome decreased by 35.8% on the 14th day of the in-patient treatment alongside with the reduction of nausea by 46.8% and diarrhea by 38.4%. The indicated findings amounted 1 point score in 45% of patients on the 30th day of the out-patient treatment; that indicated at the "lack of symptom", though bitter taste in the mouth remained in more than half a number of patients during the whole course of therapy.

"Afobazol", in contrast to "Adaptol", allowed obtaining therapeutical results as early as on the 7th day of treatment. Pain syndrome decreased by 37.2%, nausea – by 26% and bitter taste in the mouth – by 20.9%. In a month after the onset of the preparation administration 55% of patients did not complain of dyspeptic disorders.

In patients with chronic pancreatitis and MADD, who were not given psycho-pharmaco-correction, chronic pancreatitis treatment was ineffective. Patients were discharged with complaints on the apparent stomach-ache of psycho-genic nature, nausea and altered defecation pattern. Thus, MADD may provide developing of drug resistance and negative therapeutic outcome for patients with chronic pancreatitis,

Dynamics evaluation of anxio-depressive disorders in the context of administration of psycho-tropic drugs gave an opportunity to reveal a significant decrease of anxiety level on the 7th day of "Adaptol" and "Afobazol" administration; their values went down by 20.5% ($p<0.05$) and 28% ($p<0.05$) respectively. Depression level tended to decrease on the 30th day of therapy. A significant decline of reactive and personal anxiety was registered on the 14th day in the context of "Adaptol" and "Afobazol" administration, however, in 30 days of treatment "Afobazol" influence on situational anxiety was more evident and amounted 32.4±3.5 points, whereas "Adaptol" decreased reactive anxiety level up to 42.6±1,6 points only.

Research results aimed at the assessment of tranquilizers impact on the psycho-physiological functions in railroad workers demonstrated certain peculiarities. In the context of "Adaptol" administration the time of a simple motor response test performance increased by 32% comparing to the initial level ($p<0.05$), and decision-making time to green light tended to increase by 27% comparing to the same value on the 14th day of treatment. The obtained alterations support the fact that preparation has a potential to reduce rate of visual-motor reactions that restricts use of the given medication in locomotive crew workers.

"Afobazol", on the contrary, reduced time of task performance. This manifested in the decrease of a simple motor response values by 22.8% ($p<0.05$), a complex motor response to green light values by 30.2% ($p<0.05$), to red light by 25.4% ($p<0.05$), a reaction to a moving object values by 19.5% ($p<0.05$). The obtained results have an important significance for railroad workers, whose professional activity demanded boosting attention span and reaction fast rate. Positive "Afobazol" impact on the rate of visual-motor reactions has become a reason for execution of a patent for invention ("Way of increasing psycho-motor reaction rate using "Afobazol" anxiolytic", patent № 2528110, registration date 16.07.2014) [35]; conducted psycho-physiological research study gives an opportunity to determine an effective and safe preparation for

railroad workers when performing pharmacological correction of anxio-depressive disorders.

Based on pharmaco-economic analysis and considering high efficiency and low cost of the course treatment a therapy design including anxiolytic "Afobazol" is considered to have higher priority.

To conclude, it is necessary to report that results of the current study have practical significance for patients with combine pathology including chronic pancreatitis and anxio-depressive disorders, since conducted complex assessment of the gastrointestinal status, peculiarities of psycho-emotional sphere and psycho-physiological functions give an opportunity to determine pathogenic peculiarities of co-morbid diseases and choose the most rational scheme of pharmaco-correction.

Conclusions.

1. Combination of chronic pancreatitis and anxio-depressive disorders provide worsening of pain syndrome and gastro-intestinal disorders resulting in resistance to the conducted therapy.
2. Anxio-depressive syndrome, co-morbid with chronic pancreatitis, reduces rate of visual-motor reactions increasing performance time of a simple motor reaction by 45%, a complex motor reaction by 37% and a reaction to a moving object in 2 times comparing to similar findings of patients with chronic pancreatitis without anxiety disorders.
3. Complex therapy including administration of a tranquilizer "Adaptol" provides regress of anxiety on the 7th day of treatment, gastroenterological symptoms on the 14th day of treatment, whereas an "Afobazol" anxiolytic simultaneously eliminates both - anxiety and gastroenterology disorders, on the 7th day of treatment.
4. "Afobazol" anxiolytic administration as a part of complex therapy in case of exacerbation of chronic pancreatitis ensures elevated rate of visual-motor reactions in 80% of patients, whereas "Adaptol" tranquilizer affects psycho-physiological findings in 65% of cases.
5. Additional administration of an "Adaptol" tranquilizer increases treatment cost in 2.4 times, whereas application of "Afobazol" increases treatment cost in 1.4 times.

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