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Chronic Pancreatitis, Comorbid with Alcohol Addiction: Epidemiology, Causes, Developmental Features, Symptoms and Supportive Pharmaceutical Therapy

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Abstract. Chronic pancreatitis is a chronic inflammatory disease of the pancreas, which is accompanied by irreversible structural changes in the development of excretory and incretory insufficiency, manifested by abdominal pain and characterized by a significant reduction in the quality of life of patients. Purpose of the study was to determine the place of alcoholic (toxic) chronic pancreatitis among pancreatitis; to systematize scientific sources on the role of psychoactive substances in the development of comorbid chronic pancreatitis with alcohol addiction. In the period from 1997 to 2021, a review of the scientific literature on the topic of the work was conducted. Depending on the region, up to 70% of acute pancreatitis and up to 90% of chronic pancreatitis cases are alcohol-related psychoactive substances. Alcoholic (toxic) pancreatitis occurs due to exposure of the pancreas to alcohol in up to 80% of all cases. Pharmacotherapy of chronic pancreatitis is important in the context of the spread of coronavirus infection, in most cases conservative, is carried out taking into account the causes and risk factors. Scientific sources on the topic of the work are systematized. Literature data on the epidemiology, causes of chronic pancreatitis and the role of psychoactive substances in the development of chronic pancreatitis were studied.

Keywords: chronic pancreatitis, comorbid, alcohol addiction, organization and management of pharmacy, clinical pharmacy.

Introduction. Pancreatitis is a collective term that combines a group of diseases characterized by inflammation of the tissue of the pancreas (pancreas). Acute pancreatitis (AP) is an acute inflammation of the pancreas, is polyetiological, occurs due to autolysis of pancreatic tissues by activated pancreatic enzymes and manifests itself in a wide range of morphological changes - from pancreatic edema to pancreatic necrosis. Chronic pancreatitis (CP) is a chronic inflammatory disease of the pancreas, accompanied by irreversible structural changes (fibrous, cystic, to atrophic), the development of excretory and incretory insufficiency, manifested by abdominal pain and characterized by a significant decrease in quality of life.

Current world data show an increase in the number of patients with both acute pancreatitis and chronic pancreatitis. The incidence of CP in European countries ranges from 5 to 10 per 100,000 population. In general, the world has a tendency to increase the incidence of CP over the past 30 years more than 2 times [1-4].

Common factors of CP are alcohol; biliary processes (metabolic disorders, obstructive processes, trauma); idiopathy (uncertain factors); other causes of chronic inflammation of the pancreas (autoimmune diseases, genetic disorders, drugs, radiotherapy, smoking, tropical conditions). Among the generally accepted three main etiological causes of pancreatitis (alcoholic, biliary and idiopathic), alcohol is given key importance.

In Western Europe and the United States, biliary pancreatitis is thought to be acute. This is due to the fact that in the first episode of biliary pancreatitis on the background of gallstone disease, surgical treatment is performed, and as a result, this pancreatitis does not develop into chronic. In Ukraine, patients are often not operated on for a long time and thus develop chronic pancreatitis. In Ukraine, chronic biliary pancreatitis is quite common. Gallstone disease is the cause of more than half of the cases of CP in Ukraine. Also, the development of chronic biliary pancreatitis can be prevented or significantly reduce the risk of its formation with timely cholecystectomy. Idiopathic factor in the development of CP is considered and classified as idiopathic chronic inflammation of the pancreas, if all possible causes are excluded. Idiopathic chronic inflammation of the pancreas accounts for 10-20% of all cases of pancreatic disease. In some cases, idiopathic CP can be misdiagnosed for the following reasons: latent use of a psychoactive substance alcohol or hypersensitivity to a small amount of psychoactive substance alcohol, trauma, genetic causes [5-7].

Among the causes of alcoholic CP is comorbid addictive dependence on psychoactive substance alcohol. CP of alcoholic etiology is most common in people suffering from alcohol addiction for a long time. Usually, CP develops after 10 years of alcohol abuse, in women this period is reduced by 1.5 times. Defeat of the pancreas in alcohol dependence sometimes leads to dysfunction of the islet apparatus, which causes the development of comorbid insular insufficiency [8-11].

Alcoholic pancreatitis is a significant medical problem. The significance of this problem depends on the level of alcohol consumption in a country. Depending on the region, up to 70% of cases of acute pancreatitis and up to 90% of cases of CP are related to the abuse of psychoactive substance alcohol [12-14].

The purpose of the research was to determine the place of alcoholic (toxic) CP among pancreatitis; to systematize scientific sources on the epidemiology, causes of CP, the role of psychoactive substances in the development of CP, as well as to study some features of development, symptoms, and pharmacotherapy of CP, comorbid with alcohol addiction within the organization and management of pharmacy and clinical pharmacy.

Materials and methods. In the period from 1997 to 2021, a review of the scientific literature on the topic of the work was conducted. The information base consisted of foreign and domestic scientific papers [15-24]. Methods of normative-legal, documentary, retrospective, comparative, forensic-pharmaceutical, system and graphic analysis were used to process the results.

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circulation from the standpoint of forensic pharmacy and organization of pharmaceutical business" (state registration number D/21U000031, terms 2021-2026).

Results and discussion. Usually CP develops among middle-aged people (35-50 years). Patients with CP make up 25% of the total number of visits of doctors of gastroenterological offices of polyclinics of Ukraine, and in specialized gastroenterological hospitals – up to 12% of beds. Among patients with CP in 30% of cases develop early complications (purulent-septic, bleeding from gastroduodenal ulcers, thrombosis in the portal vein, etc.), mortality is 5.1%. With the further development of CP, especially with ineffective treatment, functional insufficiency of the pancreas progresses, and abdominal ischemic syndrome also develops. Pancreatic disease in more than 10% of cases is the cause of disability in patients with digestive pathology [25, 26].

Depending on the region, up to 70% of GPs and up to 90% of CP cases are alcohol-related psychoactive substances. Clinical cases are common when hospitalized patients have anamnestic data and clinical symptoms of CP comorbid with alcoholism. Periodic exacerbations of CP on the background of alcohol withdrawal syndrome or drunkenness have also been registered [27, 28].

Chronic inflammation of the pancreas often begins as a recurrence of acute inflammation of the pancreas, but in some patients' acute pancreatitis is absent in the history. Not all patients develop CP after recurrent AP. Re-inflammation of the pancreas is characterized by clear manifestations with periods of recovery between episodes. The place of alcoholic (toxic) CP among other types of inflammation of the pancreas is shown in Fig. 1.

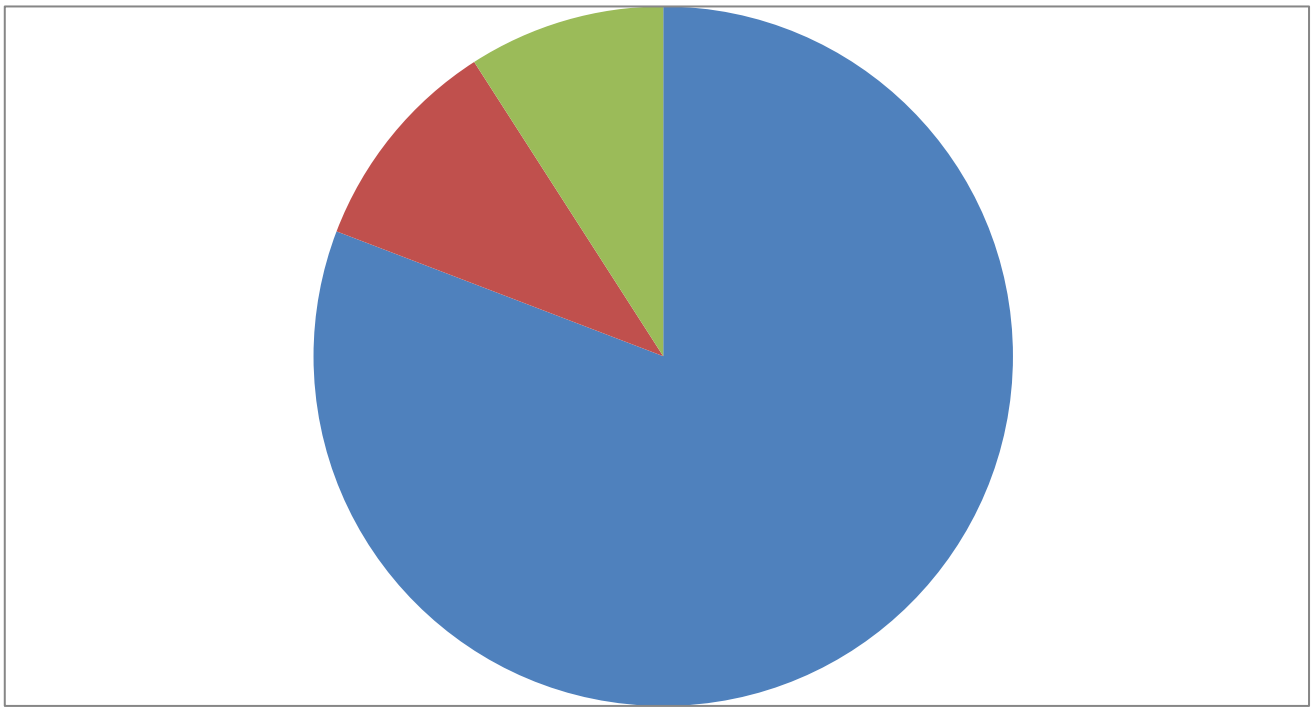

Fig. 1. The place of alcoholic (toxic) CP among other inflammations of the pancreas.

Alcoholic (toxic) pancreatitis – occurs due to exposure of the pancreas to alcohol in up to 80% of all cases. Autoimmune pancreatitis occurs due to Sjogren's disease,

primary biliary cirrhosis, and other autoimmune diseases, less than 9% of all cases. Hereditary pancreatitis occurs when there is a certain genetic predisposition. However, usually only one predisposition is not enough for the development of the disease, there must still be the influence of a causal factor. There are also several mechanisms of pathogenesis of pancreatitis. One of the most important is the increase in pressure in the duct system, which leads to damage to the epithelium and trigger mechanisms of enzyme activation in the software. Another mechanism, no less important, is the formation of protein precipitates in the small ducts of the pancreas (alcohol, senile, due to starvation). Chronic calcifying pancreatitis accounts for 50-95% of all forms and is associated with alcohol consumption. And another mechanism of pathogenesis of pancreatitis, which is still poorly understood, is the mechanism of pathogenesis of viral infections. This is not auto-digestion, but pancreatic cell dystrophy and accelerated apoptosis, which leads to the progression of fibrosis [29].

Addictive dependence. Addictive dependence on psychoactive substances is comorbid not only against the background of CP, but also other disorders. Thus, current epidemiological studies in the United States indicate a high frequency of combination of addiction from psychoactive substances (alcohol, drugs) and mental disorders: "double disorders" occur in 37% of people with mental illness, which is five times more than general population. Lifelong comorbidity was found in disorders of the schizophrenia group – 47% of patients; affective disorders – 32%; depressive disorder – 30%; bipolar affective disorder – 60.7%; anxiety disorders – 23.7%; panic disorder – 35.8%; obsessive-compulsive disorder – 32.8%; personality disorders – almost 50%; antisocial personality disorder – up to 80% of patients [30].

According to the literature, a comprehensive study of 359 men aged 30-54 years of the second stage of alcoholism associated with comorbid chronic therapeutic pathology – CP (control group consisted of 405 patients with alcoholism who were not diagnosed with chronic therapeutic disorders), proved the development of such pathology is motivational with the struggle of conscience (75%); without a struggle of conscience (13.6%); insurmountable (8%); loss of situational control in a state of intoxication (21.6%). Half of the "psychiatric" patients coming to the ambulance abuse psychoactive substances, and about 30% – due to the effects of addiction. When seeking help in the hospital, dependence is found in 30% of patients with bipolar disorder and 15-20% with schizophrenia. The study of the prevalence of comorbidity among the population of addicts shows a high frequency of anxiety and affective disorders in the irrational use of psychoactive substances, but approximately similar to the prevalence in the general population of patients in the period of restraint. There are no data on the prevalence of comorbidity in the CIS countries. In domestic psychiatry and narcology, the coverage of the problem of comorbidity is mainly descriptive, with little emphasis on the development of special approaches in treatment, pharmacotherapy, and rehabilitation. The combination of addictology and mental disorders is considered mainly from the standpoint of forensic psychiatry and forensic pharmacy in connection with aggression and suicidal behavior in a state of intoxication [30, 31].

Among the psychoactive substances most often used are those that are available and legal. Thus, about 84% of "psychiatric" patients smoke cigarettes and 40% smoke

more than 40 cigarettes daily; 17% use more than 600 mg of caffeine daily. Tobacco and caffeine are the most commonly abused alcohol, followed by banned psychoactive substances: marijuana, opiates, and amphetamines. Also used drugs – benzodiazepines and correctors of extrapyramidal disorders (cyclodol) [32, 33].

Alcohol abuse occurs in approximately 50% of all cases of CP. This percentage among patients with acute pancreatitis under the age of 39 is growing even more. With untimely treatment of patients and, as a consequence, untimely diagnostic identification of alcohol dependence, withdrawal syndrome, alcoholic pancreatitis, as well as untimely medical care, the probability of alcoholic delirium and surgery on vital pancreatic indicators increases sharply. In almost every clinical case of pancreatitis in patients with alcohol addiction there is a post-alcoholic liver function disorder. Among the symptoms of alcoholic CP, the main complaint of patients, in addition to the traditional clinic of hangover symptoms, are pain in the subcutaneous and peri-bundle areas. Most often it is a dull constant pain, a feeling of distension and discomfort in the upper abdomen. The pain is usually exacerbated after alcohol consumption, dietary inconsistencies, eating fatty foods, overeating [34].

Consider the symptoms of CP. In the recurrent form of CP on the background of constant dull pain there are attacks of acute pain in the subcutaneous area, which are often shrouding in nature. The intensity of pain during an attack may not differ significantly from the pain of acute pancreatitis. It is usually combined with varying degrees of pain on palpation in the subcutaneous and mesogastric regions. Dyspeptic disorders in such patients are primarily associated with impaired external secretory function of the pancreas. The picture of blood at the combined pathology (CP + alcohol dependence) is nonspecific and can in some cases not go beyond physiological norm. Signs of hyperchromic, macrocytic (B12-deficient) anemia may be detected in some patients with CP. With exacerbation may increase ESR, neutrophilic leukocytosis, a moderate increase in alanine and asparagine aminotransferases (ALT, AST), a moderate increase in the third fraction of lactate dehydrogenase (LDH-3), alpha-2 globulins and protein abusive, -lymphocytes and suppression of their functional activity, the tendency to increase the number of B-lymphocytes, increase the content of immunoglobulins G, A and M and the concentration of circulating immune complexes, increase trypsin, anti-trypsin, amylase, amylase, blood lipase. At disturbance of incretory function of a pancreas hyperglycemia and glucosuria are defined. In more severe cases, electrolyte metabolism may be impaired. When the head of the pancreas compresses the common bile duct, biochemical signs of cholestasis appear: an increase in total and bound bilirubin, cholesterol, bile acids, alkaline phosphatase and gamma-glutamyltranspeptidase. Ultrasound is very helpful in diagnosing pancreatitis. The main ultrasound and other radiation tomographic signs of CP are diffuse or focal increase in echogenicity of the pancreas with clear visualization of the surrounding vessels, increase or decrease its size, heterogeneity of structure, fuzzy contours. Cysts are defined as echonegative areas of oval shape with clear contours [29, 35].

Our next task was to analyze the methods of pharmacotherapy of CP accompaniment described in the literature. Pharmacotherapy of CP is important in the context of the spread of coronavirus infection, in most cases conservative, is carried

out taking into account the causes and risk factors. In the period of exacerbation, it is advisable to carry out treatment in a hospital. The main purpose of pharmacotherapy of CP, comorbid with alcohol addiction, in the period of exacerbation is:

1) mandatory elimination of the causative factor (basic therapy);
2) detoxification for therapy used in addiction;
3) relief of abdominal pain;
4) correction of external and internal secretory insufficiency of the pancreas;
5) planned anti-alcohol therapy [36-38].

Basic pharmacotherapy is manifested in adherence to diet and cessation of psychoactive substances of alcohol and nicotine. The primary metabolite of ethanol and tobacco smoke is acetaldehyde, which has a much greater toxic effect on cells than ethanol. A number of studies have shown that smoking not only exacerbates abdominal pain of pancreatic origin, but also increases the external secretory activity of the pancreas, which in the period of exacerbation of chronic alcoholic pancreatitis is highly undesirable. The basis of drug therapy outside the periods of exacerbations are polyenzyme drugs (digestive) [39, 40].

Among the physiotherapeutic methods recommended are electrophoresis of the pancreas with magnesium sulfate, zinc sulfate, novocaine, diadynamic and sinusoidal modulated currents, ultrasound, laser therapy and others.

In general, the amount of pharmacotherapy depends on the duration of intoxication, the severity of alcohol withdrawal syndrome, the presence of other comorbid pathologies, the duration of alcoholism on the background of CP, the degree of functional insufficiency of the pancreas at the time of hospitalization, other forms of pathology. for example, smoking as a pathology that exacerbates the clinical picture of combined pathology).

In the pharmacotherapy of CP, comorbid with alcohol addiction, an important place is given to the relief of alcohol withdrawal syndrome when combined with pathology of vital organs. Alcohol withdrawal relief on the background of CP is based on an integrated combination of alcohol withdrawal relief with symptomatic addition to the pharmacological complex of "tangential means and methods", i.e., aimed at the simultaneous elimination of comorbid pathology.

At defeat of a pancreas in the form of pancreatitis of alcoholic etiology in complex stopping therapy include the corresponding traditional symptomatic antipancreatic pharmacotherapy.

In clinical practice, the relief of alcohol withdrawal syndrome (alcohol withdrawal syndrome) in patients with exacerbation of chronic alcoholic pancreatitis is a difficult task due to the need for a comprehensive integrated approach involving various specialists (narcologist, psychiatrist, gastroenterologist, endocrinologist, surgeon, and endocrinologist). With the use of traditional coping methods of alcohol withdrawal syndrome or intoxication with comorbid CP, significantly increases the therapeutic resistance and risk of aggravation of withdrawal and intoxication disorders, as well as the transformation of CP from mild exacerbation to life-threatening condition.

Means of pain relief are antispasmodics: nitroglycerin under the tongue, peripheral M-cholinolytics and others. [40].

At a long pain syndrome analgesics and nonsteroidal anti-inflammatory drugs, less often non-narcotic, or narcotic analgesics (no more than 2-4 days) are used. Morphine is not used because it causes spasm of the sphincter of Oddi and causes an increase in pressure in the ducts of the pancreas. In the presence of persistent pain prescribe baralgin 5 ml 3 times a day [14].

A number of measures have been proposed to relieve abdominal pain, including the use of pancreatic secretion inhibitors such as somatostatin and enkephalins. In addition, given the close relationship between the nature of the acid-forming function of the stomach and the severity of clinical manifestations of CP, antisecretory drugs should be used, among which proton pump inhibitors are paramount [25].

In severe hyperenzymemia with persistent pain, if this condition does not help digestive and antispasmodics, then use intravenous proteolysis inhibitors (contrikal, trasilol, gordox) [12].

Compensation for external secretory insufficiency of the pancreas provides stabilization of the inflammatory process. Polyenzyme drugs are prescribed during or immediately after a meal. The daily dose ranges from 4 to 12 or more pills per day (until the therapeutic effect is achieved), with a reduction in remission to the minimum effective with the subsequent transition to reception as a preventive measure) [11].

Beta-blockers can be used to inhibit the exocrine function of the pancreas [10].

In case of intoxication, Hemodes, Reopolyglucin, Reosorbilact are prescribed, plasmaphoresis or hemosorption is performed [8].

The disadvantage of such pharmacotherapy regimens is on the one hand – polypragmatism, on the other – insufficient involvement in the therapeutic process of pathogenetic mechanisms of alcoholic pancreatitis, relatively low efficiency, and relatively long duration of treatment [7].

There is also a method of detoxification pharmacotherapy to relieve alcohol withdrawal syndrome using the enterosorbent atoxil, which is recommended for comorbid liver and pancreatic disorders [41].

Atoxyl is a silicon dioxin and is a light amorphous white powder, tasteless and odorless. One of the forms of release – glass bottles with a capacity of 250 ml. One vial contains 12.0 of finely divided silicon dioxide powder. The area of active sorption is more than 400 m^2 per 1 g of dry matter. Atoxyl is an enterosorbent with pronounced adsorption properties, has detoxifying and antimicrobial action. Adsorbs from the digestive tract and removes from the body endogenous and exogenous toxic substances of various origins, has high adsorption activity against microorganisms and proteins, including microbial toxins. Atoxyl promotes transport from the internal environment of the body (blood, lymph, interstitium) into the digestive tract due to concentration and somatic gradients of various toxic products, including medium molecules, oligopeptides, amines, and other substances with their subsequent excretion from the body [42].

There is also a method of pharmacotherapy of chronic alcoholic pancreatitis with a combination of citrarginine and atoxil. Citrarginine is administered in 10 ml twice a day per os and atoxil 4 g three times a day 1 hour before meals for 10 days. This combination of drugs helps to reduce clinical manifestations, functional disorders of

the pancreas and liver, correction of blood lipid spectrum, improving the results of sonography [43].

There is a known method of pharmacotherapy of CP of alcoholic origin using cholinolytic and antispasmodic drugs (atropine, platyphylline, gastrocepin, no-spa, papaverine) in combination with antacids (almagel, phospholugel) and H2-blockers of histamine receptors, histamine receptors.

Antibiotics are used for severe exacerbations or abscesses of the pancreas (ampiox 2 mg 4 times a day for 7-10 days, or cefoperazine 1-2 g 2 times a day).

Another method of pharmacotherapy for chronic alcoholic pancreatitis is the use of antioxidant components (vitamins A, E, selenium, etc.). Aminocaproic acid may also be used. In patients with CP, a decrease in the concentration of vitamins A, D, E and K in the serum may be observed. Such pharmacotherapy has been shown to reduce the level of damage in pancreatitis [21, 38].

In order to potentiate the effects aimed at reducing and eliminating pain, use modern antispasmodics and analgesics (mostly non-narcotic), which have universal properties to relieve abdominal pain, especially in cases of ischemia, perineural inflammation and fibrosis. The choice of drug depends on the degree of pain. The most commonly used are drotaverine (non-selective myotropic antispasmodic), mebeverine (selective myotropic antispasmodic, sodium channel blocker), pinaveria bromide (selective calcium channel blocker) and hyoscine butyl bromide (neurotropic spasm).

A significant problem in the treatment of CP is concomitant spastic disorders, dysfunction of the sphincter of Oddi, especially his hypertension. Selective antispasmodics are most often used to treat these conditions [20].

Known in the literature scheme of pharmacotherapy for chronic alcoholic pancreatitis, aimed at restoring functions damaged by ethanol, normalization of protein and fat metabolism, optimization of synthesis and secretion of bile, associated with the reception of herbal remedies containing flavonoids (drug hofitol).

Hofitol is a medicinal product, a natural product of plant origin, it is an extract from the aqueous extract of fresh artichoke leaves. The main mechanism of action of hofitol is a combination of pharmacological effects. It has the following pharmacological effects: hepatoprotective effect (flavonoids), cholelytic effect in combination with the action aimed at reducing the content of lipids in the blood (caffeolic acids); mild diuretic action (sesquiterpene lactones). Particular attention is paid to flavonoids, which are part of the drug. Flavonoids induce liver microsomal systems; stabilize hepatocyte membranes; block the transport of toxins; bind free radicals: stimulate the synthesis of proteins and phospholipids; stabilize the amount of glutathione; block the formation of acetaldehyde. The use of hofitol reduces cholesterol synthesis, which is a key factor in reducing steatosis; normalizes the metabolism of phospholipids, normalizes the lipid profile, reduces the level of atherogenic functions; increases choloresis without causing excessive contraction of the gallbladder [44].

There is a scheme of pharmacotherapy based on the phytocomposition of the functional food product Biofiton as an anti-inflammatory and choleretic hepatoprotective agent. Biofiton has the ability to improve the antitoxic function of the liver, also helps to optimize and prevent diseases of the liver and biliary tract (cholecystitis, hepatitis, cholangitis), including duodenitis, enterocolitis and digestive

disorders. The composition of biophyton includes: cumin flowers (have the ability to improve bile secretion, eliminate spasm of the gallbladder, bile ducts and intestines, also reduce bilirubin and cholesterol in the blood, extremely effective in reducing bile viscosity, activate the secretory capacity of the pancreas and antibacterial, and action); chamomile flowers (have antimicrobial, anti-inflammatory, anti-allergic, analgesic, antispasmodic effect, stimulate bile secretion and secretory activity of the digestive glands, able to normalize metabolism and effectively improve blood circulation); milk thistle fruits (have the ability to improve the detoxification function of the liver, including alcohol poisoning, neutralizing toxins, promote better bile secretion, also improve the absorption of nutrients, improve liver cell regeneration, have wound-healing, anti-inflammatory, enhance and activate) ; peppermint leaves (have astringent and antispasmodic, sedative, antiseptic and antiemetic effects); columns with corn stigmas (increase the secretion and secretion of bile, reduce its viscosity, reduce the tone of the gallbladder, increase diuresis, lower blood sugar); herb three-part (has a pronounced antimicrobial effect, anti-inflammatory and anti-allergic, emollient, diuretic, hemostatic, regenerating effect; anti-inflammatory agent that improves digestion when taken orally in diseases of the liver and gallbladder, as well as colitis, gastritis, effective food allergies); dandelion roots (improve digestive processes, have a weak choleretic, diuretic, antispasmodic and laxative effects) [40, 44].

According to the set of pharmacological effects, the described pharmacotherapy regimens are used to increase the effectiveness and reduce the time of elimination of alcohol withdrawal syndrome on the background of CP.

Thus, a comprehensive review of pharmacotherapy regimens for patients with CP, comorbid with alcohol withdrawal syndrome, to improve their quality of life.

Conclusions. Scientific sources on the topic of the work were systematized within the organization and management of pharmacy and clinical pharmacy. The place of chronic pancreatitis among pancreatitis has been determined. Literature data on the epidemiology, causes of chronic pancreatitis and the role of psychoactive substances in development of chronic pancreatitis have been studied. Some peculiarities of development, symptoms, and pharmacotherapy of chronic pancreatitis comorbid with alcohol addiction have been studied.

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