Alcoholic Hepatitis: An Experimental Meta-Analysis

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Abstract. Addictive drug dependence from psychoactive substances (alcohol, narcotics, psychotropics) with comorbid disorders against the background of the pandemic is a problem of the health care system of the world. Drugs for pharmacotherapy of alcoholic hepatitis were presented according to the criteria of effectiveness and availability. The author concluded that Prednisolone, Ursodeoxycholic acid, and Pentoxifylline received the largest amount of positive feedback. The results of the meta-analysis were recommended for doctors providing primary, secondary (specialized) medical care. Further research into the pharmacotherapy of addictive disorders due to the abuse of psychoactive substances is ongoing.
Keywords: addictive dependence, psychoactive substances, alcohol addiction, alcoholic hepatitis, forensic pharmacy, pharmacotherapy, meta-analysis, treatment protocols, standards.

Introduction. Addictive dependence is formed with the simultaneous use of psychoactive substances of different classification and legal groups. Psychoactive substances include psychoactive drugs, narcotic drugs, psychotropic substances, alcohol, alcohol-containing liquids, and alcoholic beverages. Addictive dependence is widespread on the background of infectious (COVID-19, monkeypox virus, etc.) and comorbid (psychiatric, narcological, cardiology, gastroenterological, HIV/AIDS, etc.) diseases in accordance with International Classification of Diseases (ICD-11) and the updated edition of International Classification of Diseases (ICD-11). The World Health Organization emphasizes the problem of public health security due to the spread of addictive dependence. [1-7].

Therefore, it has become relevant to research this type of addictive dependence, such as the alcohol addiction. Alcohol dependence develops with the abuse of psychoactive substances of different classification and legal groups with alcohol preparations, alcohol-containing liquids, and alcoholic beverages. At the same time, comprehensive studies on the factors of the formation and development of addictive dependence based on forensic pharmacy have not been conducted in Ukraine until now. Alcohol dependence is accompanied by the development of alcoholic hepatitis and other comorbid disorders.

The purpose of the study was to study the pharmacotherapy of alcoholic hepatitis through an experimental meta-analysis on the criteria of efficiency and availability.

Materials and methods. The study was conducted from January 2019 to December 2022. In the work, the author used the literary sources of leading scientists who used the key words alcoholic hepatitis, treatment, pharmacotherapy, drugs, treatment protocols, treatment standards in their works. The search strategy was based on the combination of terms for alcoholic hepatitis with a variant of the arbitrary text. In addition, lists of literary sources and modern systematic reviews on the topic of the work were considered. The review of scientific sources of the world's leading scientists on the formation, development and spread of addictive dependence, alcohol dependence, alcoholic hepatitis was conducted. More than 700 scientific sources on the topic of the work were used. The forensic and pharmaceutical practice of addictive dependence, alcohol dependence, alcoholic hepatitis (more than 300 cases) was analyzed. Systematized psychoactive alcohol-containing liquids (more than 210), psychoactive alcohol preparations (more than 140), psychoactive combined preparations (more than 70), alcoholic beverages (more than 70). The information base of the study consisted of scientific works of foreign and domestic scientists on the topic of the article (more than 700).

The review of scientific sources of literature was carried out taking into account the recommendations of the Cochrane Society for PICO: P (population) – the population of patients with addictive dependence, alcohol dependence, alcoholic hepatitis; I (intervention) – recommendations for clinical and pharmacological examination of patients with addictive dependence, alcohol dependence,

alcoholic hepatitis; C (comparison) – comparison in research technology, experimental study; O (outcomes) – research results. Based on a review of published qualitative strategy and management research, the author identifies highly innovative academic articles, that is, a study that demonstrates substantial novelty in every part of the research process. The author works through these articles in detail to demonstrate their novelty, highlighting concrete ways in which scholars have innovated three interconnected parts of the research process: data generation, data analysis, and presentation of findings.

For the meta-analysis, drugs for pharmacotherapy of alcoholic hepatitis were selected according to clinical protocols and standards: Code K 70.1 for ICD-11*;* Code D97 for International Classification of Primary Care-2-E *(*ICPC-2); Code DB94.1 for ICD-11.

To achieve this goal the main method was meta-analysis. Simultaneously with the meta-analysis, the methods of normative and legal, forensic pharmaceutical, documentary, comparative, graphical and tabular analysis were used. Microsoft Excel (descriptive characteristics: minimum and maximum value, average value) was used to process the results and determine the consistency between the studied parameters.

The study is a fragment of the research works of the Kharkiv Medical Academy of Postgraduate Education on the topics "Improvement of the organizational and legal procedure of providing drugs to patients from the position of forensic pharmacy, organization and management of pharmacy" (state registration No. 0116U003137, implementation period 2016-2020), "Pharmaceutical and medical law: integrated approaches to the drug circulation system from the standpoint of forensic pharmacy and the organization of the pharmaceutical case" (state registration No. 0121U000031, implementation period 2021-2026) and Petro Mohyla Black Sea National University on the topic “Conceptual interdisciplinary approaches to the drug circulation system, taking into account organizational and legal, technological, biopharmaceutical, analytical, pharmacognostic, forensic and pharmaceutical, clinical and pharmacological, pharmacoeconomic, pharmacotherapeutic aspects” (state registration No. 0123U100468, implementation period 2023-2028).

Results and discussion. To the problem of pharmacotherapy of addictive health disorders (narcotics, alcohol, etc.) with a combined diagnosis (comorbid, polymorbid, concomitant diseases) in different periods were devoted the works of various domestic and foreign scientists: Trachtenberg I.M., Stefanov O.V., Lynskii I.V., Voloshyn P.V., Minko O.I., Sosin I.K., Chuiev Yu.F., Shapovalov V.V., Haiduchok I.G., Anderson P., Bouman W.P., Chapman M. and others. The issues of the organization of pharmaceutical business, drug technology, clinical and forensic pharmacy in order to increase the level of medical care and pharmaceutical support for patients were covered in the publications of Gromovyk B.P., Ponomarenko M.S., Tolochko V.M., Trokhymchuk V.V., Volokh D.S., Shapovalov V.V. and others [8-13].

Alcohol dependence is a serious problem for health care system all over the world. More than 7% of all cases of ill health and early deaths are caused by alcohol addiction. United Nations experts note [14]:

• 3 million people die worldwide every year due to the harmful use of alcohol, which is 5.3% of all deaths;

• harmful use of alcohol is a causal factor of more than 200 diseases and injuries;

• a total of 5.1% of the global burden of disease and injury is attributable to alcohol, as measured by disability-adjusted life years (DALYs);

• alcohol consumption causes death and disability at a relatively early age. In the 20-39 age group, approximately 13.5% of the total number of deaths are related to alcohol consumption;

• there is a cause-and-effect relationship between the harmful use of alcohol and several mental and behavioral disorders, other non-infectious conditions, as well as injuries;

• recent cause-and-effect relationships have been established between the harmful use of alcohol and the incidence of infectious diseases such as tuberculosis, as well as the course of HIV/AIDS;

• in addition to health consequences, harmful use of alcohol causes significant social and economic losses to individuals and society.

Alcohol abuse during the COVID-19 pandemic deepens medico-pharmaceutical, socio-economic, forensic-pharmaceutical risks worldwide, in the USA, EU countries, Great Britain, the

Islamic Republic of Iran, and Ukraine. Thus, studies show that American men more often than women [15]: drink alcohol (56.5% vs. 47.9%, respectively); abuse alcohol (30.4% vs. 16%, respectively); engage in excessive drinking (9.9% vs. 3.4%, respectively).

A short-term increase in alcohol consumption during the COVID-19 pandemic in the United States may significantly increase long-term morbidity and mortality in the population [16].

Even moderate alcohol consumption increases the long-term risk of heart disease, liver disease, and cancer. Frequent heavy drinking can lead to alcohol dependence and comorbid disorders. Excessive alcohol consumption is a direct cause of alcoholic hepatitis. Alcoholic liver disease at the initial stage manifests itself as fatty liver, and then develops into alcoholic hepatitis, fibrosis, and cirrhosis of the liver. Alcohol abuse promotes the overgrowth of intestinal bacteria and causes changes in the microbial composition of the intestines. Antifungal treatment improves liver damage caused by alcohol. Alcohol-induced changes in gut microbes can affect physical activity and cognitive abilities, increasing the propensity to drink alcohol, further contributing to the vicious cycle of alcoholic liver damage. Alcohol consumption destroys the intestinal barrier, increases intestinal permeability, causes bacterial translocation, reduces the body's immune properties, and increases the risk of comorbid disorders [17-23].

Today there are herbal preparations for the pharmacotherapy of alcoholic pancreatitis (silymarin, quercetin, hesperidin and berberine). Known natural compounds that improve lipid metabolism in the liver. Curcumin, the main active ingredient in turmeric, reduces lipid accumulation in hepatocytes and subsequent steatosis. Dihydroquercetin, one of the most common dihydroflavonoids, is widely found in milk thistle and onions. Tanshinone is found in large quantities in the root of salvia miltiorrhiza. Among the natural compounds that reduce oxidative stress, the hepatoprotector silymarin (Silybum marianum) is known. Silymarin mainly repairs liver damage by alleviating lipid peroxidation and oxidative stress. The antioxidant activity of isorientin in buckwheat was confirmed in comparison with some antioxidants (α-tocopherol, ascorbic acid, and other compounds of plant origin). The hepatoprotective and antioxidant properties of oleanolic acid (contained in large quantities in fruits, vegetables, and herbs) have been proven. Known natural compounds that suppress inflammation due to alcoholic hepatitis. Anthocyanins are a group of plant pigments that are widely present in flowers, fruits, and cereals. Baicalin from Scutellaria baicalensis is widely used in the pharmacotherapy of alcoholic hepatitis. Corosolic acid (2α-hydroxyursolic acid) is found in banaba leaves. Corosolic acid attracted considerable attention due to its antidiabetic effect and was called "phytoinsulin". Gastrodin is one of the main bioactive components of the ancient Chinese medicinal plant Geranium Gastrodia elata. Ursolic acid also exhibits antioxidant, anti-inflammatory, anti-cancer and hepatoprotective properties. Berberine (a quaternary ammonia compound derived from many herbs) is widely used to treat liver lesions. Naringenin and naringin (the main flavanones in pomelo fruit) can effectively reduce oxidative stress, inflammation, and liver damage. Hesperidin (flavonoid in citrus peel) reduces oxidative stress and inflammation in alcoholic hepatitis. Quercetin (found in fruits and vegetables) also exhibits antioxidant properties in liver damage. Licorice has a strong prophylactic effect in chronic and acute alcoholic liver damage. Lycopene (tomatoes, watermelon, pink grapefruit, papaya, apricot, and guava) is known for its antioxidant, immunoprotective potential. Limonoids (natural tetracyclic triterpenoids with various biological properties) have shown anticancer, antiviral, and hepatoprotective effects [24-28].

In general, phytotherapy for alcoholic hepatitis has advantages. Natural compounds, easily removed from the body due to reduced bioavailability and rapid metabolism.

Thus, silymarin preparations are widely used in the United States as liver protectors, with limited toxicity and side effects. However, it is necessary to note the disadvantages of phytotherapy for alcoholic hepatitis. The clinical efficacy of most natural compounds is limited by their low bioavailability. Without standardized pharmaceutical technology, it is difficult to determine the most appropriate drug form and dosage. Most herbal medicines have not been subjected to double-blind placebo-controlled clinical trials to evaluate their effectiveness. The mechanisms of action of phytopreparations require further study.

A compelling study of more than 100,000 patients by the Veterans Health Administration found that patients with alcoholic pancreatitis and hepatitis due to alcohol and other substance abuse have difficulty accessing appropriate pharmacotherapy. Hepatitis C is a virus that affects the liver and is

spread through infected blood. In recent years, the most common cause of new hepatitis C infections is the abuse of injectable psychoactive substances (narcotic, psychotropic) in combination with alcohol, spices, volatile solvents, and tobacco smoking. Most cases are asymptomatic, but over time the disease can cause liver damage and inflammation, leading to scarring or cirrhosis and liver cancer. Complications of cirrhosis can be life-threatening and require a liver transplant. It is also a concern that patients with addictive disorders, as well as minority patients (those who identify as black or Hispanic), have barriers to accessing appropriate pharmacotherapy [29, 30].

Similar risks of pharmacotherapy of alcohol addiction, alcoholic hepatitis, and comorbid disorders exist in the USA as well [31, 32]. International recommendations suggest the use of two key drugs – prednisolone and pentoxifylline [33-35].

According to the Office for National Statistics, it has been proven that during the COVID-19 pandemic in Great Britain there was a record increase in mortality from alcoholic hepatitis [36]. Against the background of the COVID-19 pandemic in Iran, an increase in the number of deaths from alcohol addiction has been recorded [37].

According to the Ministry of Health of Ukraine, 10-35% of patients with alcohol addiction are diagnosed with alcoholic hepatitis [38]. Timely prevention, diagnosis and pharmacotherapy of hypertension will significantly improve the quality of medical services and reduce the costs of medical care. At the primary level of providing medical care to patients with alcoholic hepatitis, the family should prescribe measures to correct lifestyle, observe the regime of nutrition, work, and rest. It has been proven that complete abstinence from alcohol intake is the most important component of the success of therapeutic intervention in alcoholic hepatitis, which allows to reduce the rate of liver damage, improve the prognosis, and minimize complications in patients.

In our experiment, a meta-analysis for the analysis of direct and indirect comparisons of drugs' International Nonproprietary Name (INN) for the pharmacotherapy of alcoholic hepatitis was conducted using a multivariate meta-analysis model with statistical software STATA 13 (StataCorp, College Station, Texas, USA). A recent update to the multivariate meta-analysis procedure in STATA enables network meta-analysis to be performed in commonly used meta-analysis software.

The design of the research design is presented in Table. 1.

Table 1. Design of the research.

No.	Stage	Type of work
1.	Regulatory and legislative analysis of protocols for the treatment of alcoholic hepatitis in Ukraine, Kazakhstan, Europe	Collection and analysis of drugs' INNs used for pharmacotherapy of alcoholic hepatitis using the database of the Ministry of Health of Ukraine, Medelement, Duodecim Medical Publications Ltd.
2.	Ranking of drugs' INNs for the pharmacotherapy of alcoholic hepatitis according to the criteria of *effectiveness*	Conducting a survey of doctors to determine the specific share of the value of drugs' INNs in various treatment protocols according to the criteria of *effectiveness*
3.	Ranking of drugs' INNs for the pharmacotherapy of alcoholic hepatitis according to the criteria of *availability*	Conducting a questionnaire of doctors to determine the percentage of the value of drugs' INNs in various legislative and regulatory acts according to the criteria of *availability*
4.	Construction of a comparison network of INN drugs for the pharmacotherapy of alcoholic hepatitis, considering the criteria of *effectiveness* and *availability*	Conducting a meta-analysis to analyze direct and indirect comparisons of drugss' INNs for the pharmacotherapy of alcoholic hepatitis using a multivariate meta-analysis model with STATA 13 statistical software
5.	Conclusions	Determination of conclusions based on comparison network analysis

In the database of Duodecim Medical Publications Ltd, as of December 2021, there is no information and official translations of international clinical protocols on the pharmacotherapy of alcoholic hepatitis. Therefore, based on the provisions of the unified clinical protocol of primary, secondary (specialized) medical care "Alcoholic hepatitis" (approved by the order of the Ministry of Health of Ukraine dated 06.11.2014 No. 826) and the clinical protocol for the diagnosis and treatment of liver cirrhosis in adults (Approved by the Joint Commission with of the quality of medical services of the Ministry of Health of the Republic of Kazakhstan dated April 29, 2021 No. 135) with the help of regulatory and documentary analysis of the current legislation of Ukraine, the regulatory and legal characteristics of drugs for the pharmacotherapy of alcoholic hepatitis were provided (Table 2).

Table 2. Regulatory and legal characteristics of drugs for the pharmacotherapy of alcoholic hepatitis.

No.	INN	Protocol in Ukraine	Protocol in Kazakhstan[2]	National list[3]	State forumalar[4]	OTC list[5]
1.	S-adenosylmethionine[6]	+		-	-	-
2.	Pentoxifylline	+		-	+	-
3.	Prednisolone	+		+	+	-
4.	Tocopherol acetate (vitamin E)	+		-	+	+
5.	Ursodeoxycholic acid	+	+	-	+	-
6.	Sofosbuvir		+			
7.	Azathioprine		+			
8.	Budesonide		+			
9.	Velpatasvir		+			
10.	Voxilaprevir		+			
11.	Glecaprevir		+			
12.	Grazoprevir		+			
13.	Daclatasvir		+			
14.	Calcium carbonate, Cholecalciferol (vitamin D3)		+			
15.	Carvedilol		+			
16.	Lactulose		+			
17.	Ledipasvir		+			
18.	Losartan		+			
19.	Methylprednisolone		+			
20.	Metformin		+			
21.	Ombitasvir / Paritaprevir / Ritonavir + Dasabuvir		+			
22.	Pibrentasvir		+			
23.	Pioglitazone		+			
24.	Prednisone		+			
25.	Propranolol		+			
26.	Ribavirin		+			
27.	Rifaximin		+			
28.	Rifampicin		+			
29.	Spironolactone		+			

30.	Tenofovir alafenamide fumarate		+			
31.	Tenofovir disoproxil fumarate		+			
32.	Torasemide		+			
33.	Fenofibrate		+			
34.	Furosemide		+			
35.	Elbasvir		+			
36.	Entecavir		+			

Legislative basement (Table 2):

1 – Order of the Ministry of Health of Ukraine dated November 6, 2014 No. 826 "On the approval and implementation of medical and technological documents on the standardization of medical care for chronic non-infectious hepatitis";

2 – Order of the Joint Commission on the Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan dated April 29, 2021 No. 135 "Clinical Protocol for Diagnosis and Treatment of Liver Cirrhosis in Adults";

3 - Resolution of the Cabinet of Ministers of Ukraine dated March 25, 2009 No. 333 "Some issues of state regulation of prices for medicinal products and medical products", which approved the "National List of Essential Medicinal Products";

4 – Order of the Ministry of Health of Ukraine dated April 22, 2021 No. 792 "On approval of the thirteenth edition of the State Formulary of Medicines and ensuring its availability";

5 – Order of the Ministry of Health of Ukraine dated April 18, 2019 No. 876 "On Approval of the List of Medicines Allowed for Use in Ukraine, Which Are Dispensed Without Prescriptions from Pharmacies and Their Structural Subdivisions";

6 – The active substance is not registered in Ukraine as a drug, it exists only as a special food product.

According to the regulatory and legislative analysis, none of the 36 drugs is simultaneously included in all the specified regulatory documents. For the pharmacotherapy of alcoholic hepatitis, four drugs and a special food product S-adenosylmethionine are used. Only Prednisone is included in the National List of Essential Medicines. Only tocopherol acetate (vitamin E) was included in the list of over-the-counter drugs approved for use in Ukraine. Ursodeoxycholic acid is used for pharmacotherapy of alcoholic hepatitis in Ukraine and Kazakhstan.

According to the clinical-pharmacological group, drugs for the pharmacotherapy of alcoholic hepatitis belong to the following ATS classification codes: A05 – drugs used in diseases of the liver and biliary tract; A11 – vitamins; C04 – peripheral vasodilators; H02 – corticosteroids for systemic use. According to the classification and legal feature, the listed drugs belong to the general group, and according to the nomenclature and legal feature, Pentoxifylline, Prednisone and Ursodeoxycholic acid belong to the prescription group, are issued according to the prescription of f-1, and Tocopherol acetate (vitamin E) belongs to the non-prescription group.

To carry out the next stage of the research on the ranking of INN drugs for the pharmacotherapy of alcoholic hepatitis according to the efficiency criterion, a questionnaire was conducted among doctors to determine the specific share of the INN drug value in various treatment protocols.

Doctors of a therapeutic profile who conduct pharmacotherapy of patients with alcoholic hepatitis were invited to answer the questions of the questionnaires (Tables 2, 3).

Thus, the respondents answered that the availability of drugs for the pharmacotherapy of alcoholic hepatitis in the INN databases is mostly very important (range from 70% to 93%).

Table 2. Questionnaire for doctors regarding the ranking of INN drugs for the pharmacotherapy of alcoholic hepatitis according to the criterion of *effectiveness*.

No.	Question	Answer
1.	In your opinion, how important is the presence of INN drugs for the pharmacotherapy of alcoholic hepatitis	88 % – very important 12% – mediocre

	in the protocol of the base of the Ministry of Health of Ukraine (Ukraine)	0% – not important
2.	In your opinion, how important is the presence of INN drugs for the pharmacotherapy of alcoholic hepatitis in the protocol of the Medelement database (Kazakhstan)	70 % – very important 18% – mediocre 12% – not important
3.	In your opinion, how important is the presence of INN drugs for the pharmacotherapy of alcoholic hepatitis in the protocol of the Duodecim Medical Publications Ltd database (International)	93 % – very important 7% – mediocre 0% – not important

To carry out the research stage regarding the ranking of the INNs of drugs for the pharmacotherapy of alcoholic hepatitis according to the criteria of availability, the questionnaire was conducted among doctors to determine the percentage of the INNs of drugs of various legislative and regulatory acts (Table 3).

Table 3. Questionnaire for doctors regarding the ranking of INN drugs for the pharmacotherapy of alcoholic hepatitis according to the *availability* criteria.

No.	Question	Answer
1.	In your opinion, how important is the availability of INN drugs for the pharmacotherapy of alcoholic hepatitis in the Resolution of the Cabinet of Ministers of Ukraine dated March 25, 2009 No. 333 "Some issues of state regulation of prices for medicinal products and medical products", which approved the "National List of Essential Medicinal Products";	78% – very important 12% – mediocre 10% – not important
2.	In your opinion, how important is the availability of INN drugs for the pharmacotherapy of alcoholic hepatitis in the Order of the Ministry of Health of Ukraine dated April 22, 2021 No. 792 "On approval of the thirteenth edition of the State Formulary of Medicines and ensuring its availability";	87% – very important 13% – mediocre 0% – not important
3.	In your opinion, how important is the availability of INN drugs for the pharmacotherapy of alcoholic hepatitis in rhe Order of the Ministry of Health of Ukraine dated April 18, 2019 No. 876 "On Approval of the List of Medicines Allowed for Use in Ukraine, Which Are Dispensed Without Prescriptions from Pharmacies and Their Structural Subdivisions"	77 % – very important 7% – mediocre 16% – not important

The respondents answered that the availability of drugs for the pharmacotherapy of alcoholic hepatitis in the INN databases is mostly very important (range from 77% to 87%). Considering the data of the questionnaire, graphs were built using software.

The next stage of the research was the construction of a network of comparison of INN drugs for the pharmacotherapy of alcoholic hepatitis, considering the criteria of effectiveness and availability. To do this, a meta-analysis was conducted to analyze direct and indirect comparisons of INN drugs for the pharmacotherapy of alcoholic hepatitis using a multivariate meta-analysis model with statistical software STATA 13 (Fig. 1).

For the study, only INN drugs for the pharmacotherapy of alcoholic hepatitis were selected, which are included in the unified clinical protocol of primary, secondary (specialized) medical care "Alcoholic hepatitis" (approved by the order of the Ministry of Health of Ukraine dated November 6, 2014, No. 826).

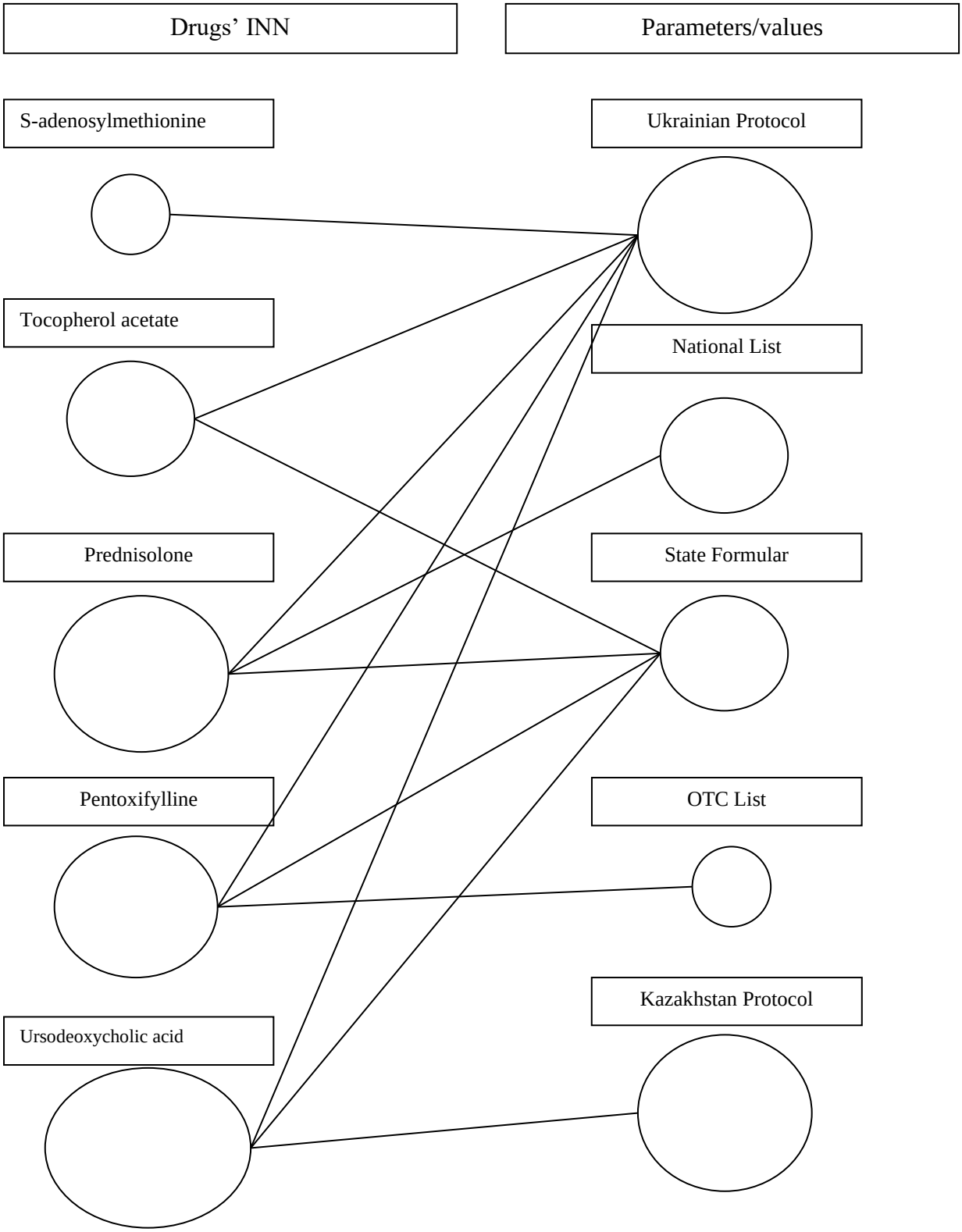

Fig. 1. The network of comparison of INNs drugs for the pharmacotherapy of alcoholic hepatitis, considering the criteria of *effectiveness* and *availability.*

Only questionnaire data with the most informative answers were selected for the study.

Group-level data were used in the network meta-analysis. Binomial probability was used for dichotomous outcomes and normal probability was used for continuous outcomes. Study effect sizes were then synthesized using a random-effects network meta-analysis model. Correlations due to multigroup studies using multivariate distributions were considered. Dispersion in the distribution of random effects (dispersion of heterogeneity) was considered a measure of the degree of inter-study and

intra-comparative variability of drugs' INNs. In addition, the network meta-analysis indicated that the degree of heterogeneity is the same for all drugs' INNs.

Conclusions. Well-founded that against the background of the COVID-19 pandemic, addictive dependence on psychoactive substances (alcohol, narcotics) with comorbid disorders is a problem of the health care system in the world. The causes and consequences of alcoholic hepatitis have been proven. A review of herbal preparations for the pharmacotherapy of alcoholic hepatitis was conducted. Treatment protocols were analyzed. The experimental meta-study presented a comprehensive and transparent picture of the hierarchy among INN drugs for the pharmacotherapy of alcoholic hepatitis according to the criteria of effectiveness and availability. Concluded that Prednisolone, Ursodeoxycholic acid, and Pentoxifylline received the largest amount. The results of the meta-analysis are recommended for doctors providing primary, secondary (specialized) medical care for the pharmacotherapy of alcoholic hepatitis. Further research into the pharmacotherapy of addictive disorders due to the abuse of psychoactive substances is ongoing.

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