Clinical and Pharmacological, Organizational and Legal, Forensic and Pharmaceutical Research of Drugs of ATC-Group N01AX03 for Anesthesia

Alina Osyntseva (PhD in Pharmaceutical Sciences, Luhansk State Medical University, Public Organization "Association of medical and pharmaceutical law", both – Ukraine)
*Corresponding author: Alina Osyntseva

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Abstract. Clinical and pharmacological, organizational and legal, forensic and pharmaceutical study of drugs of the N01AX03 group for anesthesia was conducted. A clinical and pharmacological research based on the results of a documentary analysis in a retrospective measurement of indicators of clinical-pharmaceutical safety of ketamine showed that ketamine became the first non-inhalation anesthetic. It causes dissociative anesthesia with an analgesic effect. It is used in emergency surgery, during evacuation in combat conditions, in cardiac surgery, dentistry, ophthalmology, otorhinolaryngology, gynecology. It is prescribed for patients with traumatic shock and blood loss. The organizational and legal research based on the results of the study of the marketing, classification, legal, nomenclature and legal indicators of drugs with ATC code N01AX03 showed the circulation on the pharmaceutical market of Ukraine of 4fourpsychotropic, prescription drugs of ketamine in the form of ampoules and vials for intramuscular and intravenous administration. Forensic and pharmaceutical research based on the results of the study of the control regime, availability, cases from forensic pharmaceutical practice, legal responsibility for the illegal circulation of drugs with ATS code N01AX03 made it possible to establish a direct relationship between the indicated indicators.

Keywords: pharmacy organization and management, clinical pharmacy, forensic pharmacy, control regime, anesthetics, ketamine.

Introduction. Pain of various genesis experienced by patients suffering from traumatological, oncological, narcological, comorbid health disorders cause the need for proper and timely medical and pharmaceutical care against the background of coronavirus and other infectious diseases [1-9].

Today, in Ukraine, the system of guaranteed patient access to drugs of clinical and pharmacological, classification and legal, nomenclature and legal groups is not sufficiently developed. We have a particularly low level of availability for different contingents of patients of prescription drugs, psychoactive drugs and those that are subject to subject-quantitative accounting [10-17].

Thus, providing patients with medicines for general anesthesia remains a problematic issue. Postoperative pain is pain experienced by a patient after surgery. Postoperative pain management is an important aspect of anesthesiology. One of the recommended drugs for the treatment of postoperative pain is ketamine.

The purpose of the study was clinical and pharmacological, organizational and legal, forensic and pharmaceutical study of drugs of the ATC-group N01AX03 for anesthesia.

Materials and methods. The study was conducted from December 01, 2022 to March 20, 2023. The clinical and pharmacological study was conducted using the document analysis in the retrospective measurement of indicators of clinical and pharmaceutical safety of ketamine. Organizational and legal research was conducted by studying the marketing, classification and legal, nomenclature and legal indicators of drugs of ATC code N01AX03. Forensic and pharmaceutical research was conducted by studying the regime of control, availability, cases from forensic and pharmaceutical practice, legal responsibility for the illegal circulation of drugs with ATC code N01AX03. ATC code N01AX03 includes drugs for anesthesia, such as ketamine. More than 50 normative acts were analyzed; 100 sources of scientific literature on the topic of work; 33 instructions for medical use of drugs of group N01AX03; 25 cases from forensic pharmaceutical practice [18-29].

Documentary, retrospective, normative and legal, clinical and pharmacological, classification and legal, nomenclature and legal, forensic and pharmaceutical, comparative and graphic methods of analysis were used.

The research of the article is a fragment of research works of Kharkiv Medical Academy of Postgraduate Education on "Improving the organizational and legal procedure for providing patients with drugs from the standpoint of forensic pharmacy, organization and management of pharmacy" (state registration number 0116U003137, terms 2016-2020) and "Pharmaceutical and medical law: integrated approaches to the system of drug circulation from the standpoint of forensic pharmacy and organization of pharmaceutical business" (state registration number 0121U000031, terms 2021-2026); 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 number 0123U100468, implementation period 2023-2028); Luhansk State Medical University "Conceptual interdisciplinary approaches to pharmaceutical provision and availability of drugs, taking into account organizational and legal, technological, analytical, pharmacognostic, forensic and pharmaceutical, clinical and pharmacological, pharmacoeconomic, marketing, social and economic competencies" (state registration number 0123U101632, terms 2023-2027).

Results and discussion. A retrospective and documentary analysis showed that ketamine is used in medicine and veterinary medicine for anesthesia.

Clinical and pharmacological study of ketamine. Ketamine was synthesized in 1962 by the American researcher Stevens S. It was first used in the clinic in 1965 by doctors Corssen and Domino. In the late 1960s, the drug was used in American soldiers who were in the Vietnam War. Ketamine was approved for medical use in 1970 in the USA. Forensic and pharmaceutical analysis showed that from 1987 to 2000, twelve deaths related to ketamine overdose were registered in the USA and Europe. Ketamine became the first non-inhalation anesthetic. The drug was used in psychiatric and other scientific studies [30-33].

Ketamine is a structural analogue of phencyclidine. Ketamine inhibits the function of neurons in the cerebral cortex and thalamus. In this case, functional disorganization occurs in the midbrain and thalamus. This condition is called dissociative anesthesia. Clinical and pharmacological analysis characterizes this state by the fact that the patient seems to be awake (opens eyes, swallows, muscles contract), but he is not able to analyze sensory stimuli and respond to them [34-36].

Ketamine binds to opioid receptors in the brain and spinal cord, which may explain its pain-relieving effect. After intravenous administration, ketamine causes anesthesia in 30-60 seconds, which lasts 10-15 minutes. With intramuscular injection, ketamine causes anesthesia after 3-4 minutes, which lasts 15-25 minutes. In this case, dissociative anesthesia occurs: the patient's eyes can be open, the pupils are moderately dilated, many reflexes are preserved, but they are not protective. Characterized by increased tone of skeletal muscles, lacrimation and hypersalivation (increased salivation). Uncontrolled movements of the limbs, torso, and head, independent of surgical manipulations, are possible. Amnesia often lasts up to 1 hour after regaining consciousness. With the introduction of ketamine, blood pressure increases by an average of 25%. Ketamine can significantly increase pulmonary artery pressure, pulmonary vascular resistance. Ketamine dilates cerebral vessels, increases cerebral blood flow (by about 60%), brain oxygen consumption and intracranial pressure. In the body, ketamine is metabolized by demethylation. The main part of the biotransformation products is excreted in the urine within 2 hours, but a small number of metabolites can remain in the body for several days [37-38].

Ketamine is administered intravenously or intramuscularly. The analgesic effect of ketamine develops when injected into a vein within 10 minutes. and lasts approximately 2-3 hours. With intramuscular injection, the effect is longer. Ketamine is used for mononarcosis and combined anesthesia. It is indicated in emergency surgery and at the stages of evacuation, in patients with traumatic shock and blood loss during various surgical operations (including cardiac surgery). Ketamine is used in combined intravenous anesthesia, as well as in endoscopic procedures, cardiac

catheterization, minor surgical procedures, dressings, including in dental, ophthalmic and otorhinolaryngological practices. There is evidence of the successful use of ketamine in obstetric practice for caesarean section. In children, ketamine is used for induction anesthesia for various types of combined anesthesia. Ketamine can be used in combination with neuroleptics (droperidol, etc.) and analgesics (fentanyl, promedol, etc.). In these cases, the dose of ketamine is reduced. When using ketamine, it is necessary to consider the peculiarities of its general effect on the body. The drug usually causes an increase in blood pressure (by 20-30%), an increase in heart rate. Stimulation of cardiac activity can be reduced using diazepam. With rapid intravenous administration, respiratory depression is possible. To reduce salivation, atropine solution is administered. The use of ketamine may be accompanied by involuntary movements, hypertonicity, hallucinatory phenomena. These effects are prevented or removed by the introduction of tranquilizers and droperidol. With intravenous administration of a solution of ketamine, pain, and redness of the skin along the vein are sometimes possible; on awakening, psychomotor agitation and relatively prolonged disorientation are possible [39-42].

In 2019, the US Food and Drug Administration (FDA) approved the medical use of esketamine for anesthesia and pharmacotherapy of depression. Esketamine is a drug for anesthesia and pharmacotherapy of depression [43-45]. The antidepressant effect of ketamine is possibly related to the action on opioid receptors. In subjects who were simultaneously given ketamine and naltrexone (an opioid receptor antagonist), the antidepressant effect disappeared or was significantly reduced. The dissociative effect was present in full measure. In this regard, concerns have been voiced that ketamine or preparations based on it can cause addiction characteristic of opioids. Ketamine is contraindicated in patients with cerebral circulation disorders, with severe hypertension, with severe circulatory decompensation, epilepsy and other diseases accompanied by convulsive readiness. Caution should be exercised during operations on the larynx (the use of muscle relaxants is necessary) [46-48].

Organizational and legal study of ketamine. According to the WHO anatomic-therapeutic and chemical classification system (ATC codes), drugs with the international non-proprietary name (INN) of ketamine are systematized under the ATC code N01AX "Other means for general anesthesia"; code subdivision N01AX03 "Ketamine" [49]. The group of drugs N01AX03 is used for induction and basic anesthesia during short-term surgical interventions, painful instrumental and diagnostic manipulations, patient transportation, treatment of burn surfaces. Also, in anesthesiology, a combination of general anesthetics is widely used to reduce the negative effect on geodynamics, breathing and quick recovery of consciousness after anesthesia. For this purpose, an NMDA receptor antagonist (ketamine) is most often combined with a GABA receptor agonist (propofol). Such a combination provides more stable geodynamics due to the adrenergic effect of ketamine, reduces the need for narcotic analgesics due to the analgesic effect of ketamine, and provides a pleasant sleep of short duration with a quick recovery of consciousness without hallucinations because of propofol.

According to the results of the classification and legal analysis, ketamine belongs to the poisonous classification and legal group. From the moment of entry into force (from October 01, 2011) of subparagraph 2 of paragraph 1 of the amendments approved by the resolution of the Cabinet of Ministers of Ukraine dated January 05, 2011 No. 4 "On Amendments to Resolutions of the Cabinet of Ministers of Ukraine dated June 05, 2000 No. 770 and from October 10, 2007 No. 1203" expanded the list of narcotic drugs, psychotropic substances and precursors, approved by the Resolution of the Cabinet of Ministers of Ukraine dated June 05, 2000 No. 770 (with changes). List No. 2 of Table II "Psychotropic substances whose circulation is restricted" was supplemented with the item "ketamine". Thus, ketamine is included in the classification and legal group "psychotropic substances", and its circulation is carried out in accordance with the Law of Ukraine "On Narcotic Drugs, Psychotropic Substances and Precursors", i.e., the activity of ketamine circulation must be licensed. According to the nomenclature and legal sign, ketamine is dispensed from pharmacies and their structural subdivisions according to the prescription and requirements of health care institutions.

Marketing study of ketamine. The method of analysis of marketing indicators of drugs was described in [24, 50, 51]. Table 1 presents a list of drugs N01AX03 Ketamine.

Table 1. List of drugs N01A X03 Ketamine.

No.	Trade name	Pharmaceutical form	Manufacturer
1.	Yesketamine Kalceks	Solution for injections and infusions 5 mg/ml, 5 ml, No. 5	JSC "Grindex", Latvia
2.	Ketamine	Solution for injections 50 mg/ml, 2 ml, No. 10	JSC “Farmak”, Ukraine
3.	Yesketamine Kalceks	Solution for injections and infusions 25 mg/ml, 2 ml, 10 ml, No. 5	JSC "Grindex", Latvia
4.	Ketamine -ZN	Solution for injection 50 mg/ml, 2 ml, No. 10	Kharkiv Pharmaceutical Enterprise "Zdorovye Narodu" LLC, Ukraine

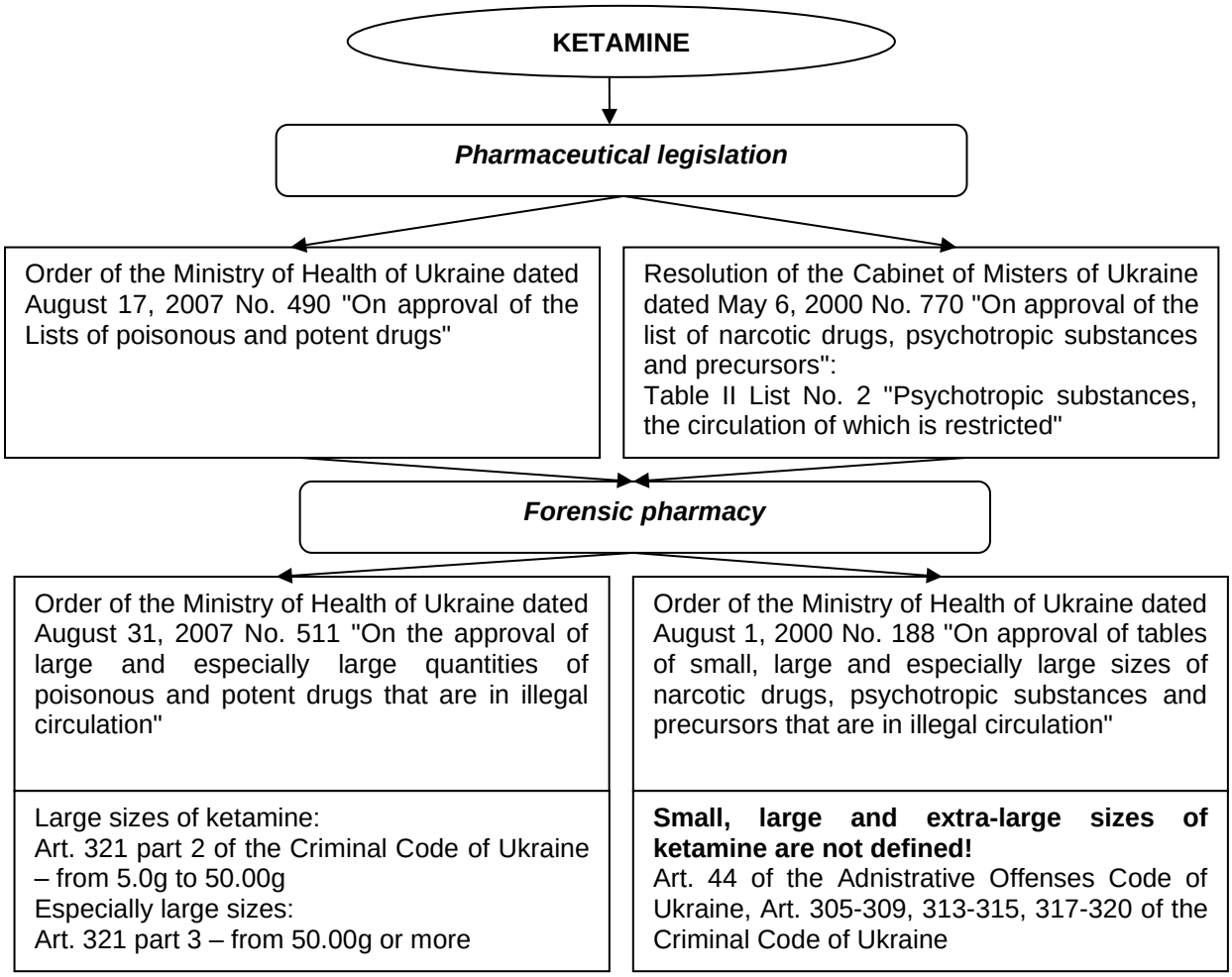
As can be seen from the data in Table. 1, ATC code N01AX03 Ketamine includes four drugs. The two drugs are produced by Ukrainian manufacturers and are available in the form of a solution for injections and infusions in ampoules, vials for intramuscular and intravenous administration.

Subsequently, the registration certificates of ketamine preparations were analyzed (Table 2).

Table 2. Validity of registration certificates of drugs N01AX03 Ketamine.

No.	Trade name	Manufacturer	Registration certificate (RP)		
			RP	Date of registration	End date of RP
1	Yesketamine Kalceks	JSC "Grindex", Latvia	UA/18939/01/01	10.09.2021	10.09.2026
2	Ketamine	JSC “Farmak”, Ukraine	UA/1934/01/01	unlimited from 28.05.2019	
3	Yesketamine Kalceks	JSC "Grindex", Latvia	UA/18939/01/02	10.09.2021	10.09.2026
4	Ketamine - ZN	Kharkiv Pharmaceutical Enterprise "Zdorovye Narodu" LLC, Ukraine	UA/12951/01/01	unlimited from 04.06.2018	

Forensic and pharmaceutical study of ketamine. Further research in the framework of forensic pharmacy was aimed at determining the responsibility for the illegal circulation of ketamine depending on the control regime (Fig. 1).



As can be seen from the Fig. 1, the responsibility for the illegal circulation of ketamine depends on the classification and legal group to which ketamine belongs. Thus, if ketamine is included in the list of poisonous drugs, criminal liability for illegal trafficking under Article 321 of the Criminal Code of Ukraine begins with 5.0 grams [52]. It is noteworthy that the Code of Administrative Offenses does not provide for liability for the illegal circulation of ketamine as a poisonous drug.

Now let us consider how the responsibility for the illegal circulation of ketamine will change when the classification and legal group is changed. In fig. 1, we see that when ketamine is included in the list of psychotropic substances, administrative responsibility appears under Art. 44 of the Code of Criminal Procedure (small quantities of psychotropic substances), and criminal liability for illegal trafficking is already determined by articles 305-309, 313-315, 317-320 of the Criminal Code. However, today we do not have in the order of the Ministry of Health of Ukraine No. 188 the corresponding values of small, large, and especially large amounts of ketamine as a psychotropic substance, which indicates the impossibility of determining administrative or criminal liability. We believe that before the implementation of the Cabinet of Ministers of Ukraine Resolution No. 4 dated January 05, 2011 "On Amendments to Resolutions of the Cabinet of Ministers of Ukraine No. 770 dated June 05, 2000 and No. 1203 dated October 10, 2007" it is necessary to first decide on these questions.

When studying the peculiarities of the formation of the nomenclature-legal group of ketamine depending on the classification-legal group, it was established that the prescription status of the drug does not change when the classification-legal group is changed (from poisonous to psychotropic), but some features must be considered (Fig. 2).

Thus, until October 1, 2011, ketamine as a poisonous drug was dispensed with a F-1 prescription from pharmacies of all forms of ownership and was subject to subject-quantitative accounting. A prescription for dispensed ketamine is kept for one year, not counting the current one.

Since the entry into force of sub-item 2 of item 1 of the amendments approved by the resolution of the Cabinet of Ministers of Ukraine No. 4 dated January 05, 2011, ketamine as a psychotropic drug is dispensed from pharmacies with a special license to permit work with narcotic, psychotropic and precursors. Dispensing is carried out according to a special F-3 prescription (the prescription for the dispensed medicine is kept for 5 years, not including the current one).

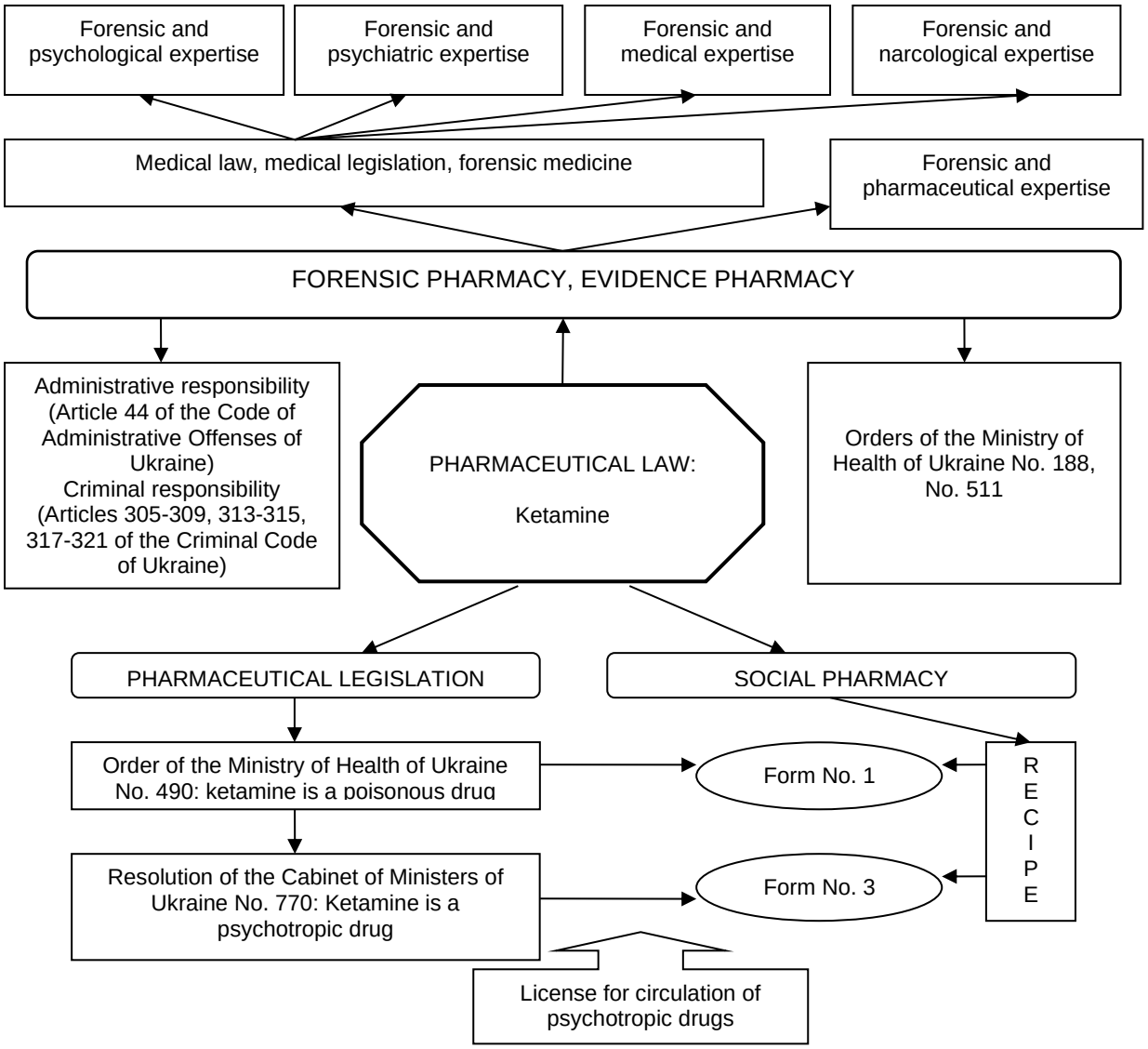


Fig. 2. Peculiarities of the formation of a nomenclature and legal group and responsibility for violations of the circulation of ketamine depending on the classification and legal group.

Such changes in the legislation can lead to stopping the sale of ketamine, depriving the population of Ukraine (in particular, pediatric patients) of the opportunity to receive the necessary medical and pharmaceutical assistance and reducing the level of availability of ketamine anesthetics for patients.

Conclusions. A clinical and pharmacological, organizational and legal, forensic and pharmaceutical study of drugs of the N01AX03 group for anesthesia was conducted. A clinical and pharmacological study based on the results of a documentary analysis in a retrospective measurement of indicators of clinical-pharmaceutical safety of ketamine showed that ketamine became the first non-inhalation anesthetic. It causes dissociative anesthesia with an analgesic effect. Used in emergency surgery, during evacuation in combat conditions, in cardiac surgery, dentistry, ophthalmology, otorhinolaryngology, gynecology. It is prescribed for patients with traumatic shock and blood loss. The organizational and legal research based on the results of the study of the marketing, classification, legal, nomenclature and legal indicators of drugs with ATC code N01AX03

showed the circulation on the pharmaceutical market of Ukraine of 4 psychotropic, prescription drugs of ketamine in the form of ampoules and vials for intramuscular and intravenous administration. Forensic and pharmaceutical research based on the results of the study of the control regime, availability, cases from forensic pharmaceutical practice, legal responsibility for the illegal circulation of drugs with ATS code N01AX03 made it possible to establish a direct relationship between the indicated indicators.

Conflict of interest. The author declares that he is the sole author of this work and has approved it for publication. The author certifies that the research was conducted in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

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References.

1. Shapovalov V. Multidisciplinary study of the level of availability of medicines for cancer patients based on the principles of pharmaceutical law, evidence-based pharmacy, clinical pharmacy, forensic pharmacy, and the organization of a pharmaceutical case. *Actual Problems of Medicine and Pharmacy*. 2023. Vol.4. No.1. P.1–20. URL: https://doi.org/10.52914/apmp.v4i1.52.

2. Osyntseva A. Cannabinoid addiction: pharmacotherapy, forensic and pharmaceutical practice, availability of drugs. *SSP Modern Pharmacy and Medicine*. 2023. Vol.3. No.1. P.1-11. URL: https://doi.org/10.53933/sspmpm.v3i1.83.

3. Shapovalova V. Forensic and pharmaceutical risks in the organization of pharmacotherapy of covid, post-covid and long-covid disorders. COVID-19 and vaccination practice standards. *SSP Modern Pharmacy and Medicine*. 2022. Vol. 2. No. 4. P.1–24. URL: https://doi.org/10.53933/sspmpm.v2i4.69.

4. Shapovalova V.A., Zbrozhek S.I., Shapovalov V.V. et al. Coronavirus disease pandemia 2019: growth of epidemic dangers. *Acta scientific pharmaceutical sciences.* 2020. Vol. 4. Iss. 7. P. 61–68. URL: https://www.actascientific.com/ASPS/ASPS-04-0559.php.

5. Shapovalov (Jr.) V., Shapovalova V., Gudzenko A. et al. Organizational and legal analysis of the pharmaceutical provision for the most common diseases of society. *International Journal of Pharmaceutical Sciences Review and Research.* 2018. Vol.51. N.1. July-August 2018. Article N. 18, P. 118-124. URL: http://globalresearchonline.net/journalcontents/v51-1/18.pdf.

6. Shapovalova V. An Innovative multidisciplinary study of the availability of coronavirus vaccines in the world. *SSP Modern Pharmacy and Medicine.* 2022. Vol.2. No.2. P.1-17 URL: https://doi.org/10.53933/sspmpm.v2i2.45.

7. Shapovalova V. Monkeypox virus – new challenges of modernity: experimental organizational and legal, clinical and pharmacological studies. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. N.3. P.1-15. URL: https://doi.org/10.53933/sspmpm.v2i3.54.

8. Smith J. Enhancing affected person care and the scope of apply for pharmacists, scholar pharmacists by immunizations throughout the monkeypox outbreak. *Monkeypox Breaking news*. 21.12.2022. URL: https://monkeypox-treatment.com/enhancing-affected-person-care-and-the-scope-of-apply-for-pharmacists-scholar-pharmacists-by-immunizations-throughout-the-monkeypox-outbreak/.

9. Nikholas. Patient care. Enhancing patient care and the scope of practice for pharmacists, student pharmacists through immunizations during the monkeypox outbreak. *Hide my health. Trending Now. HUR Siege*. 2022. URL: https://hidemyhealth.com/enhancing-patient-care-and-the-scope-of-practice-for-pharmacists-student-pharmacists-through-immunizations-during-the-monkeypox-outbreak.html.

10. Shapovalov V.V. (Jr.), Shapovalova V.A., Shapovalov V.V. Forensic and pharmaceutical research on the impact of drugs on the safety, life and health of road users within the organization of

pharmaceutical business, drug technology, pharmaceutical and medical law in Ukraine. *Health of Society*. 2021. Vol.10. No.4. P.127-132. URL: https://doi.org/10.22141/2306-2436.10.4.2021.246355.
11. Shapovalova V. The ICD-11 for the twenty-first century: the first view from the organizational, legal, clinical and pharmacological aspects. *SSP Modern Pharmacy and Medicine.* 2022. Vol.2. N.1. P.1-13. URL: https://doi.org/10.53933/sspmpm.v2i1.37.
12. Shapovalova V. Alcoholic Hepatitis: An Experimental Meta-Analysis. *SSP Modern Pharmacy and Medicine*. 2023. Vol.3. No.1. P.1-11. DOI: https://doi.org/10.53933/sspmpm.v3i1.77.
13. Shapovalova V. Interdisciplinary pharmacoeconomic research concerning the pharmacotherapy of Alcoholic Hepatitis in conditions of COVID-19 pandemic. *SSP Modern Pharmacy and Medicine*. 2023. Vol.3. No.2. P.1-10. URL: https://doi.org/10.53933/sspmpm.v3i2.87.
14. Sosin I.K., Chuev Yu.F., ArtemchukA.P., Shapovalova V.O. Shapovalov Valentyn. V et al. Narcology: national textbook. Kharkiv, Ukraine: Kolegium.2014. 948 p.
15. Shapovalova V.A., Voloshyn P.V., Stefanov A.V. et al. Medicines for neurologists, psychiatrists and narcologists. Kh.: «Fakt». 2003. 784 p.
16. Shapovalova V.A., Sosyn I.K., Butenko G.M. et al. Pharmaceutical law in narcology. Kharkiv: "Fact". 2004. 800 p.
17. Gubskyi Y.I., Shapovalova V.O., Kutko I.I. et al. Medicines in psychopharmacology. K.: "Health", Kharkiv: *"Torsing"*.1997. 288 p.
18. Shapovalov V. (Jr.), Gudzenko A., Shapovalova V. at. el. Forensic and pharmaceutical study of the presence of a causal link between the degree of alcohol abuse and qualification level of the respondents. *Pharmacia*. 2017. Vol.66. No.3. P. 31-39. URL: http://bsphs.org/wp-content/uploads/2017/11/Shapovalov.pdf.
19. Shapovalova V. A., Shapovalov V. V. Handbook of legal and forensic pharmacy. Kharkiv.: Torsing.1997. 656 p.
20. Shapovalova V., Zakharchenko I. Organizational and legal approaches to reforming of the law enforcement system of Ukraine: illegal circulation of psychoactive substances and addictive dependence. *SSP Modern Law and Practice*. 2021. Vol. 1. No.1. P.1–22. URL: https://doi.org/10.53933/sspmlp.v1i1.20.
21. Tukhar I., Shapovalova V., Shapovalov V. et al. Pharmacological view on the problem of comorbidity in the pharmacotherapy of chronic pancreatitis. *Science Review*. Vol.3. No.38. P.1-5. URL: https://doi:10.31435/rsglobal_sr/30072021/7591.
22. Shapovalov V. (Jr.), Gudzenko A., Shapovalova V. et al. Concerning the importance of forensic and pharmaceutical researches to improve patients' accessibility to medicines. *Pharmacia.* 2017. Vol.65. No.2. P.23–29. URL: http://bsphs.org/wp-content/uploads/2017/07/Shapovalov.pdf.
23. UNODC World Drug Report 2022 highlights trends on cannabis post-legalization, environmental impacts of illicit drugs, and drug use among women and youth. *Press release. UN*. Vienna. 27.06.2022. URL: https://www.unodc.org/unodc/en/press/releases/2022/June/unodc-world-drug-report-2022-highlights-trends-on-cannabis-post-legalization--environmental-impacts-of-illicit-drugs--and-drug-use-among-women-and-youth.html.
24. Chuiev Yu., Shapovalova V. Interdisciplinary pharmacoeconomic study of pharmacotherapy of cupping of drunk forms of alcohol dependence: clinical and pharmacological, organizational, legal and marketing experiment. *SSP Modern Pharmacy and Medicine*. 2021. Vol.1. No.2. P.1-12. URL: https://doi.org/10.53933/sspmpm.v1i2.24.
25. Shapovalov V.V., Gudzenko A.A., Shapovalova V., Zbrozhek S.I. et al. Forensic and pharmaceutical analysis of addictive morbidity because of the use of psychotropic psychoactive substances in Ukraine (retrospective aspect). *Annals of Mechnikov Institute.* 2018. N. 3. P. 41–44. DOI: 10.5281/zenodo.1456544. URL: http://www.imiamn.org.ua/journal/3_2018/PDF/9.pdf.
26. Shapovalova V.A., Zbrozhek S.I., Shapovalov V.V. et al. Forensic pharmacy: some risk factors in the formation of addictive health disorders. *Acta Scientific Pharmaceutical Science*. 2021. Vol.5. Iss.1. P.54-59. DOI: 10.31080/ASPS.2020.05.0651. URL: https://actascientific.com/ASPS/ASPS-05-0651.php.

27. Nehretskii S. Forensic and pharmaceutical, organizational and legal studies of illegal circulation, danger and drug addiction from cannabinoids. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. No.4. P.1-15. URL: https://doi.org/10.53933/sspmpm.v2i4.71.
28. Hayduchok I., Tukhar I., Shapovalov V. Chronic Pancreatitis, comorbid with alcohol addiction: epidemiology, causes, developmental features, symptoms and supportive pharmaceutical therapy. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. No.2. P.1-13. URL: https://doi.org/10.53933/sspmpm.v2i2.46.
29. Gelen S., Sarper N., Demirsoy U. et al. The Efficacy and Safety of procedural sedoanalgesia with Midazolam and Ketamine in pediatric hematology. *Turk. J. Hematology*. 2015. No.32. P.351-354. URL: https://pubmed.ncbi.nlm.nih.gov/25913821/.
30. Shapovalov V., Veits O. Forensic and pharmaceutical, criminal and legal, social and economic study of the conditions, that cause bribery corruption in the system of legal relations "doctor-patient-investigator-lawyer". *SSP Modern Law and Practice*. 2022. Vol.2. No.3. P.1-16. URL: https://doi.org/10.53933/sspmlp.v2i3.57.
31. Jansen K. Ketamine: Dreams and Realities. Multidisciplinary Association for Psychedelic Studies. 2001. P.23 URL: https://maps.org/images/pdf/books/K-DreamsKJansenMAPS.pdf.
32. Bonanno F.G. Ketamine in war/tropical surgery (a final tribute to the racemic mixture). Injury J. 2002. Vol.33. No.4. P.323-327. URL: Injury 2002-05: Vol 33 Iss 4: Free Download, Borrow, and Streaming : Internet Archive.
33. White P.F., Way W.L., Trevor A.J. Ketamine--its pharmacology and therapeutic uses. 1982. URL: https://pubmed.ncbi.nlm.nih.gov/6892475/.
34. Calvey N., Williams N. Principles and Practice of Pharmacology for Anaesthetists. Wiley-Blackwell. 2001. 357p. URL: https://archive.org/details/principlespracti0000calv.
35. Bergman S.A. Ketamine: review of its pharmacology and its use in pediatric anesthesia. *Anesthesia Progress Journal*. 1999. Vol. 46. No.1. P.10—20. URL: https://pubmed.ncbi.nlm.nih.gov/10551055/.
36. Olney W., Labruyere J., Price M. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science.* 1989. Vol.244. No.4910. P.1360-1362. URL: https://pubmed.ncbi.nlm.nih.gov/2660263/.
37. White P., Ham J., Way W. et al. Pharmacology of ketamine isomers in surgical patients. *Anesthesiology Journal.* 1980. Vol. 52. No.3. P. 231-239. URL: https://pubmed.ncbi.nlm.nih.gov/10551055/.
38. Grant I.S., Nimmo W.S., McNicol L.R. et al. Ketamine disposition in children and adults. *British Journal Anaesth*. 1983. Vol.55. No.11. P.1107-1111. URL: https://pubmed.ncbi.nlm.nih.gov/6639827/.
39. Elia N., Tramèr M. Ketamine and postoperative pain--a quantitative systematic review of randomised trials. *Painl*. 2005. Vol.113. No.1-2. P.61-70. URL: https://pubmed.ncbi.nlm.nih.gov/15621365/.
40. Shaprio H., Wyte S., Harris A. Ketamine anaesthesia in patients with intracranial pathology. *British Journal Anaesth*. 1972. Vol. 44. No.11. P.1200-1204. URL: https://pubmed.ncbi.nlm.nih.gov/4647115/.
41. Dawson B., Michenfelder J., Theye R. Effects of ketamine on canine cerebral blood flow and metabolism: modification by prior administration of thiopental. *Anesth Analg*. 1971. Vol. 50. No. 3. P. 443-447. URL: https://pubmed.ncbi.nlm.nih.gov/5103782/.
42. Thorsen T., Gran L. Ketamine/diazepam infusion anaesthesia with special attention to the effect on cerebrospinal fluid pressure and arterial blood pressure. *Acta Anaesthesiol Scand.* 1980.Vol. 24. No. 1. P. 1-4. URL: https://pubmed.ncbi.nlm.nih.gov/7376798/.
43. Han Y., Chen J., Zou D. et al. Efficacy of ketamine in the rapid treatment of major depressive disorder: a meta-analysis of randomized, double-blind, placebo-controlled studies. *Neuropsychiatric Disease and Treatment.* 2016. No. 12. P. 2859-2867. URL: https://pubmed.ncbi.nlm.nih.gov/27843321/.

44. Rakesh G., Pae C., Masand P. Beyond serotonin: newer antidepressants in the future. *Expert Review of Neurotherapeutics*. 2017. No. 17. P. 777—790. URL: https://pubmed.ncbi.nlm.nih.gov/28598698/.
45. Esketamine-Johnson&Johnson. 23.03.2023. URL: https://adisinsight.springer.com/drugs/800037644.
46. FDA Advisory Committee Recommends Approval of SPRAVATO™ (esketamine) Nasal Spray CIII for Adults with Treatment-Resistant Depression. *Janssen. Johnson&Johnson.* 12.02.2019. URL: https://www.janssen.com/fda-advisory-committee-recommends-approval-spravato-esketamine-nasal-spray-ciii-adults-treatment.
47. Ng J. et al. Efficacy of Ketamine and Esketamine on Functional Outcomes in Treatment-Resistant Depression: A Systematic Review. *Journal of Affective Disorders.* 2021. URL: https://www.sciencedirect.com/science/article/abs/pii/S0165032721006182.
48. Williams N., Heifets B., Blasey C. et al. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. *The American Journal of Psychiatry*. 2018. Vol.175. No.12. P.1205-1215. URL: https://pubmed.ncbi.nlm.nih.gov/30153752/.
49. Cohut M. Testing whether ketamine acts like an opioid. *Medical News Today*. 29.08.2018. URL: https://www.medicalnewstoday.com/articles/322909
50. ATC-classification. Compendium on-line. URL: http://compendium.com.ua/atc.
51. Hayduchok I., Shapovalova V., Ishcheikin K. et al. Pharmaeconomic approaches for pharmacotherapy of Rheumatoid arthritis. *Likars'ka Sprava*. 2021. No. 1–2. P.70-79. https://doi.org/10.31640/JVD.1-2.2021(11). URL: https://liksprava.com/index.php/journal/article/view/463.
52. Shapovalov (Jr.) V., Gudzenko A., Shapovalova V., Shapovalov V. Forensic and pharmaceutical analysis of addictive morbidity because of the use of narcotic psychoactive substances in Ukraine (retrospective aspect). *International Journal of Pharmaceutical Sciences and Research.* 2018. Vol. 3. Is.3. P.22-25. URL: http://www.pharmacyjournal.net/archives/2018/vol3/issue3.
53. Criminal Code of Ukraine. *Verkovna Rada of Ukraine*. URL: https://zakon.rada.gov.ua/laws/show/2341-14/page15#Text.