An Interdisciplinary Approach to Development of a New Combined Medicine for Musculoskeletal Disorders

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Abstract. Musculoskeletal disorders represent a significant global health concern, affecting millions and straining healthcare systems. Addressing the complex nature of musculoskeletal disorders necessitates a multifaceted approach, one that integrates various scientific disciplines. This paper delves into the collaborative efforts employed in the development of a new combined medication tailored for musculoskeletal disorders. Bringing together expertise from pharmacology, biomedicine, physiotherapy, and bioinformatics, the research has forged a holistic pathway to medication synthesis. Key focus areas include the evaluation of molecular targets, ensuring optimal drug-drug interactions, and tailoring the therapeutic approach based on the individual patient's needs and the specific disorder's pathology. Furthermore, insights from physical therapy informed the drug development process, ensuring that the new medication aligns with rehabilitative approaches and promotes functional recovery. Advanced computational methods also played a pivotal role, enabling the prediction of drug efficacy, potential side effects, and patient response variability. Preliminary results suggest that this interdisciplinary strategy not only enhances the drug's therapeutic potential but also minimizes adverse reactions, paving the way for a more comprehensive and effective approach to managing musculoskeletal disorders. This research underscores the power of interdisciplinary collaboration on the relevance, necessity, and timeliness of the pharmaceutical development of a new combined medicine for musculoskeletal disorders based on known active pharmaceutical ingredients. The characteristics of active pharmaceutical ingredients (ketamine, analgin, diazepam) were studied in order to substantiate the composition based on a combination of evidence-selected active pharmaceutical ingredients. The composition, clinical and pharmacological properties, control regime, availability, areas of medical application, quality and safety profile were substantiated.

Keywords: musculoskeletal system, lesion, traumatology, pharmacotherapy, pharmaceutical development, new medicine.

Introduction. The military conflict in Ukraine posed a number of challenges for medical and pharmaceutical care for persons with damage to the musculoskeletal system, skeletal damage, craniocerebral injuries, open wounds, and pathologies of internal organs. Today, the standard of analgesia for severe and moderate pain intensity is analgesia, which involves the simultaneous administration of several drugs that affect most of the chains in the formation of the pain sensation. Of all non-opioid analgesics, analgin is most often used in combination with non-steroidal anti-inflammatory drugs. Opioids are prescribed for severe pain and ineffectiveness of non-narcotic regimens. Pain relief schemes for patients with traumatic injuries include anesthesia [1].

Patients who have undergone limb amputation are in a very difficult situation. Their quality of life is significantly reduced, and the experience of phantom pain syndrome worsens their situation

even more. In order to treat phantom pains against the background of post-traumatic stress disorder, depression, covid, post-covid, long-covid disorders, it is recommended to prescribe tranquilizers, hypnotics, sedatives [2, 3].

Worth to note that the use of any medicinal products, including analgesic, anesthetic and tranquilizing drugs, should be carried out only by qualified medical professionals. The best solution is to consult a medical specialist who will be able to assess the situation and prescribe the appropriate treatment, taking into account the individual needs of each patient. Proper pharmaceutical supply with effective, high-quality, safe, and affordable drugs is important.

The search for new drugs and pharmacotherapy schemes based on a combination of evidence-selected active pharmaceutical ingredients using an interdisciplinary approach has not been conducted so far in the world and in Ukraine.

The purpose of the study was to conduct an interdisciplinary study on the relevance, necessity and timeliness of the pharmaceutical development of a new combined drug for lesions of the musculoskeletal system based on known active pharmaceutical ingredients using clinical, surgical, traumatological, clinical-pharmacological, classification-legal, nomenclature-legal, forensic-pharmaceutical, organizational and legal, marketing approaches to the justification of the composition, clinical and pharmacological properties, control regime, availability, areas of medical application, quality and safety profile.

Materials and methods. Interdisciplinary research was conducted from February 1, 2023 to August 30, 2023. The analysis of literature sources was carried out according to the topic of the study. Pharmaceutical development of a new drug based on known active pharmaceutical ingredients was carried out using previous experience [4-12]. The methods of documentary, retrospective, normative-legal, clinical, traumatological, clinical-pharmacological, classification-legal, nomenclature-legal, forensic-pharmaceutical, sociological, comparative methods of analysis were used.

The research of the article is a fragment of research works of 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); 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); Lviv Medical Institute LLC on the topic "Improving the system of drug circulation during pharmacotherapy on the basis of evidence-based forensic pharmacy, organization, technology, biopharmacy and pharmaceutical law» (state registration number 0120U105348, implementation period 2021-2026).

Results and discussion. The interdisciplinary context of expanding the possibilities of medical and pharmaceutical care at all levels for physical injuries, injuries of the locomotor system in the conditions of the factors of war events should take place both quantitatively and qualitatively. The complexity of medical and pharmaceutical care is explained by the presence of comorbid disorders in patients (neurological, mental, cardiology, gastroenterology, narcology, oncology) [13-19].

Clinical trauma studies

Wartime conditions can cause various physical damage to the locomotor system in affected persons (Table 1).

Table 1. Traumatic lesions of the musculoskeletal system and pharmacotherapy.

No.	Trauma	Cause	Pharmacotherapy
1.	Combat wounds	Military operation	Anesthetic drugs
2.	Acute pain syndromes	Stressful situations, injuries and strenuous physical activity associated with military operations	Analgesic drugs
3.	Injuries and psychological stress	Conditions of military conflict	Tranquilizing drugs

Some of them may require the use of anesthetics, analgesics, and tranquilizers to ensure the desired level of treatment and comfort. The relevance, necessity, and timeliness of the pharmaceutical development of a new drug based on known active pharmaceutical ingredients is explained by the spread of injuries of the musculoskeletal system in wartime conditions, for which anesthetic (ketamine), analgesic (metamizole) and tranquilizing (diazepam) drugs must be used.

General characteristics of the active pharmaceutical ingredient Ketamine

International and chemical names: Ketamine; 2-(ortho-chlorophenyl)-2-(methyl amino)-cyclohexanone hydrochloride.

Main physicochemical properties: transparent colorless or slightly colored liquid.

The drug Ketamine is in circulation on the pharmaceutical market of Ukraine.

The composition of the solution for injection in ampoules: 1 ml of the solution contains ketamine hydrochloride 57.6 mg (calculated as ketamine 50.0 mg); excipients: benzethonium chloride, sodium chloride, water for injections.

Clinical and pharmacological group. Means for general anesthesia. ATC code N01AX03. Pharmaceutical form – ampoules [20].

Marketing research on the active pharmaceutical ingredient Ketamine

The method of analysis of marketing indicators of drugs was developed and described earlier [21]. In the Table 2 authors present a list of drugs of N01AX03 Ketamine.

Table 2. List of drugs of ATC code N01AX03 Ketamine.

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

As can be seen from the data in the Table 2, 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 drugs were analyzed (Table 3).

Table 3. Validity of registration certificates of drugs of ATC code N01AX03 Ketamine.

No.	Trade name	Manufacturer	Registration certificate (RC)		
			RC	Registration date	Ending of the RC
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 05.28.2019	–
3.	Yesketamine Kalceks	JSC "Grindex", Latvia	UA/18939/01/02	10.09.2021	10.09.2026
4.	Ketamine-ZN	LLC Kharkiv Pharmaceutical Enterprise "Zdorovia Narodu", Ukraine	UA/12951/01/01	unlimited from 04.06.2018	–

Drugs registered and approved for circulation and medical use in Ukraine with Ketamine have an unlimited registration period (Ketamine, Ketamine-ZN) and limited to 2026 (Yesketamine Kalceks).

Clinical traumatological, clinical and pharmacological study of the active pharmaceutical ingredient Ketamine

Pharmacodynamics

Ketamine has pronounced general anesthetic and analgesic effects. The action of the active pharmaceutical ingredient Ketamine is due to inhibition of various departments of the central nervous system. The active pharmaceutical ingredient Ketamine reduces somatic pain sensitivity to a greater extent than visceral pain sensitivity, which should be taken into account during cavity operations [22].

Pharmacokinetics

The active pharmaceutical ingredient Ketamine is characterized by high solubility in lipids and rapid tissue distribution. Plasma protein binding was 12%. Metabolized in the liver. It is excreted by the kidneys, mainly in the form of metabolites, it has no cumulative effect.

The areas of clinical application of Ketamine are given in the Table 4.

Table 4. Clinical use of Ketamine.

Clinical use		
Combined and mono anesthesia for short-term surgical interventions	Emergency surgery	At the stages of evacuation of patients with traumatic shock and blood loss
In case of painful diagnostic manipulations	Indicated among patients with low blood pressure	Indicated when it is necessary to maintain independent lung ventilation

Special warnings

Ketamine is injected intravenously as a single instant or fractionally and dropwise, as well as intramuscularly. It is administered intravenously in a dose of 2-3 mg/kg regardless of the patient's age, intramuscularly in adults 4-8 mg/kg, in children 2-5 mg/kg of body weight. To maintain anesthesia, Ketamine administration is repeated in the amount of half the initial dose. Maintenance of anesthesia by continuous intravenous infusion of the drug is achieved by administration at a rate of 2 mg/kg per hour. The minimum effective dose of Ketamine when administered intravenously is 0.5 mg/kg of body weight (consciousness is lost after 1-2 minutes, the effect lasts approximately 2 minutes). In a dose of 1 mg/kg, it works for 6 minutes, 2 mg/kg – for 10-15 minutes. With intramuscular administration, the effect occurs more slowly, but it lasts longer (at a dose of 6-8 mg/kg, the effect develops after 6-8 minutes and lasts 30-40 minutes). When injected into a vein, the analgesic effect develops within 10 minutes and lasts for 2-3 hours. It should be taken into account that Ketamine increases blood pressure by 20% - 30%, accelerates the rhythm of heart contractions, and increases the minute volume of the heart. Cardiac stimulation can be reduced by diazepam [23].

Side effects and contraindications of Ketamine are given in the Table 5.

Table 5. Side effects and contraindications of Ketamine.

No.	Side effects	Contraindications
1.	On the part of the cardiovascular system, an increase in the pulse rate and blood pressure level is quite often observed.	Arterial hypertension
2.	Violation of the rhythm (depression) and frequency of breathing	Angina
3.	Phenomena of psychomotor excitement, hallucinations, increased salivation	Disorders of cerebral circulation
4.	Pain and hyperemia are noted at the injection site.	Cardiovascular failure in the decompensation stage
5.	Arterial hypertension	Preeclampsia and eclampsia
6.	From the side of the central nervous system	Epilepsy in childhood

Interaction with other medicines

Ketamine can be used together with analgesics (metamizole sodium). At the same time, the dose of Ketamine is reduced.

Storage conditions: store in a place inaccessible to children, protected from light, at a temperature of 15ºC to 25ºC.

Shelf life: 2 years.

Ketamine control regimen

Clinical and pharmacological group – for general anesthesia N01A X03 [24]. Classification and legal group – poisonous drug. Nomenclature and legal group – according to a doctor's prescription.

Therefore, it is promising to combine Ketamine in the ampoule dosage form with water-soluble analgesics and sedative tranquilizers.

General characteristics of the active pharmaceutical ingredient of Metamizole Sodium

International and chemical names: Metamizole Sodium; sodium salt of ((2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl) methylamino) methanesulfonic acid. Gross formula C13H16N3NaO4S.

Main physicochemical properties: transparent, colorless, or slightly yellowish or greenish-yellowish liquid.

Physical and chemical properties: easily soluble in water, difficult to dissolve in alcohol.

The drug Metamizole Sodium is in circulation on the pharmaceutical market of Ukraine.

The composition of the solution for injections in ampoules: 1 ml of the solution contains Metamizole Sodium 500 mg; excipients: sodium metabisulfite (E223), disodium edetate, sodium hydroxide, water for injections.

Clinical and pharmacological group. Analgesics and antipyretics. Pyrazolones. ATC code N02BB02. The dosage form is ampoules [20, 25].

Marketing research on the active pharmaceutical ingredient Metamizole Sodium

The Table 6 presents a list of drugs of N02BB02 Metamizole sodium in ampoule dosage form [26].

Table 6. List of drugs of ATC code N02BB02 Metamizole sodium

No.	Trade name	Medical form	Manufacturer
1.	Analgin	Solution for injection 500 mg/ml, 1 ml, 2 ml, No. 10	"Yuria-Pharm" LLC, Ukraine
2.	Analgin – Zdorov'ya	Solution for injections 500 mg/ml, 2 ml, 5 ml, No. 10	LLC "Pharmaceutical company "Zdorovia", Ukraine
3.	Analgin – Darnytsya	Solution for injections 500 mg/ml, 2 ml, No. 10	PJSC "Pharmaceutical firm "Darnytsia", Ukraine

4.	Analgin	Solution for injections 500 mg/ml, 2 ml, No. 10	PJSC "Lekhim - Kharkiv", Ukraine
5.	Analgin	Solution for injections 500 mg/ml, 1 ml, 2 ml, No. 10	LLC Kharkiv Pharmaceutical Enterprise “Zdorovia Narodu” (all stages of production, quality control), Ukraine

As can be seen from the data in the Table 3, five ampoule preparations assigned to ATC code N02BB02 Metamizole sodium. All of these drugs are produced in Ukraine in the form of a solution for injections in ampoules.

Subsequently, the registration certificates of ampoule preparations Metamizole sodium were analyzed (Table 7).

Table 7. Validity of registration certificates of drugs of ATC code N02BB02 Metamizole sodium.

No.	Trade name	Manufacturer	Registration certificate (RC)		
			RC	Registration date	RC ending
1.	Analgin	"Yuria-Pharm" LLC, Ukraine	UA/14166/01/01	Unlimited from 31.10.2019	–
2.	Analgin – Zdorov’ya	LLC "Pharmaceutical company "Zdorovia", Ukraine	UA/5706/02/01	Unlimited from 10.11.2016	–
3.	Analgin – Darnytsya	PJSC "Pharmaceutical firm "Darnytsia", Ukraine	UA/3222/02/02	Unlimited from 27.04.2017	–
4.	Analgin	Private joint-stock company "Lekhim - Kharkiv", Ukraine	UA/4014/02/01	Unlimited from 28.08.2017	–
5.	Analgin	Limited liability company Kharkiv Pharmaceutical Enterprise “Zdorovia Narodu” (all stages of production, quality control), Ukraine	UA/8802/01/01	Unlimited from 27.07.2018	–

Medicinal products in the form of a solution for injections, which include Metamizole sodium, contain 500 mg of the active pharmaceutical ingredient in 1 ml. Five medicinal products registered in Ukraine have an unlimited term of registration. Metamizole sodium is produced by Ukrainian pharmaceutical manufacturers.

Clinical and traumatological, clinical and pharmacological study of the active pharmaceutical ingredient of Metamizole Sodium

The pharmacodynamics of the Metamizole Sodium is shown on the Fig. 1.

Pharmacokinetics

After administration, Metamizole Sodium is hydrolyzed to an active metabolite (when administered intravenously, unchanged metamizole is detected in plasma in small amounts). The connection of the active metabolite with proteins is 50–60%. Metabolized in the liver, excreted by the kidneys. It is quickly and evenly distributed in tissues. The maximum concentration is reached 1-1.5 hours after intramuscular administration. The elimination half-life (T1/2) is about seven hours. Excreted with urine.

The areas of clinical application of Metamizole Sodium are shown on the Fig. 2.

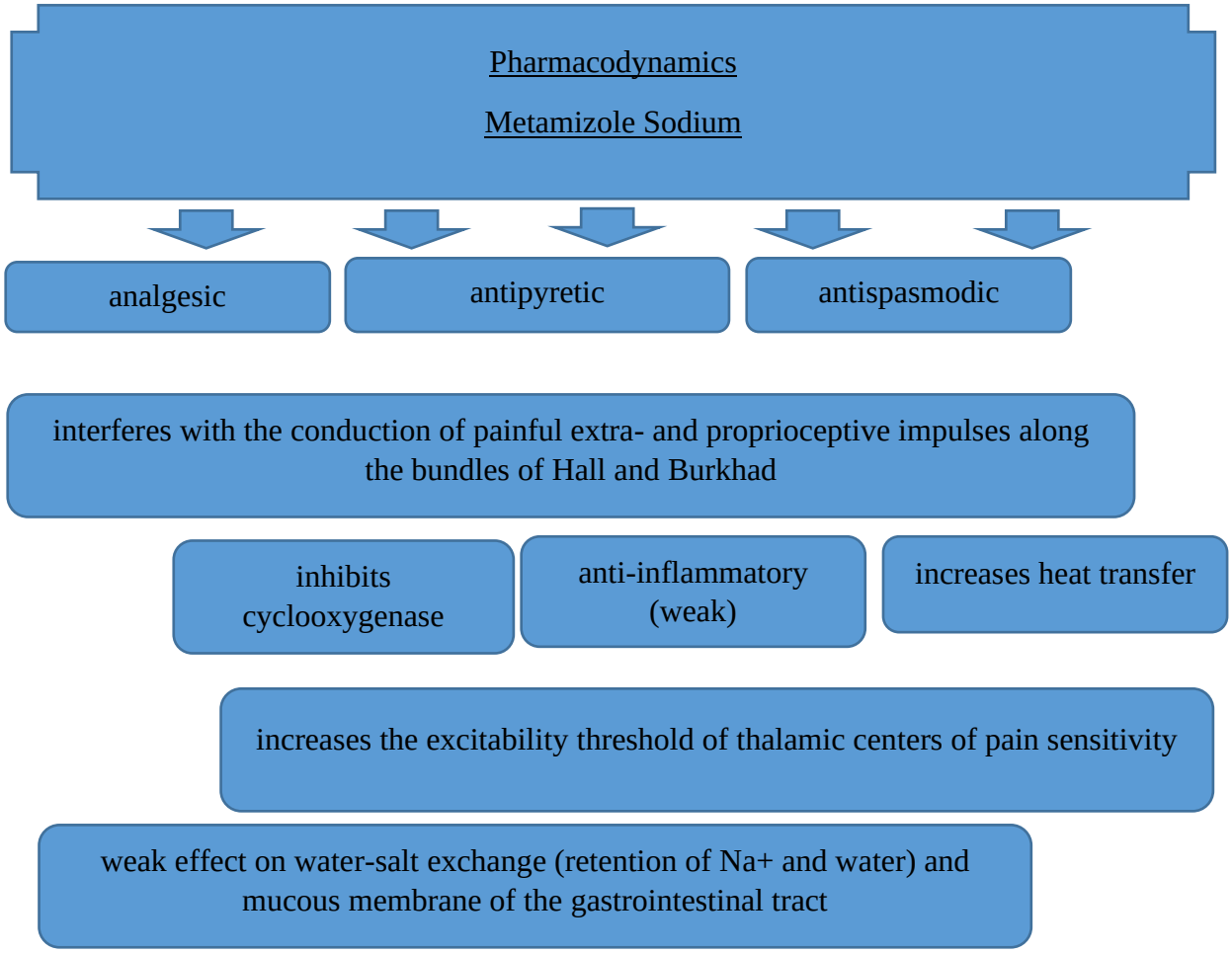

Fig. 1. Pharmacodynamics of Metamizole Sodium.

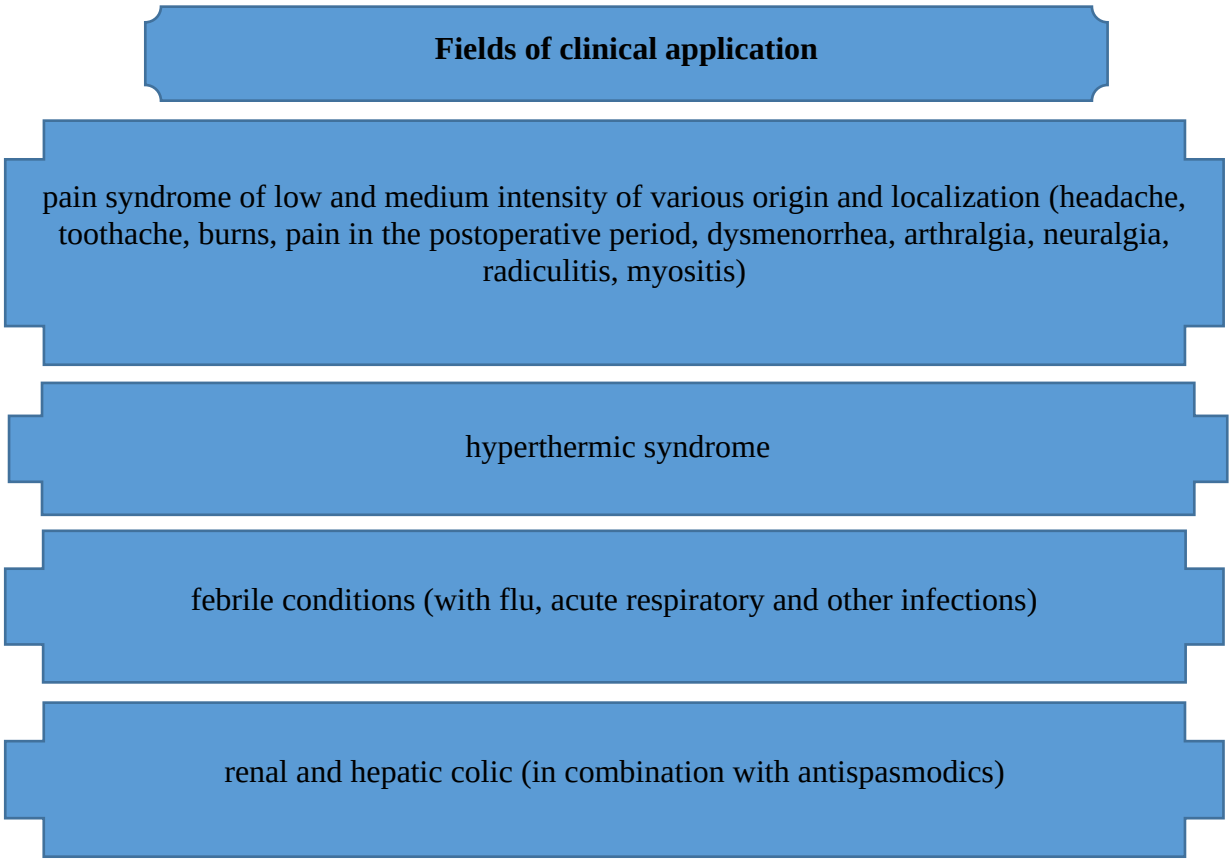

Fig. 2. Applications of Metamizole Sodium.

Special warnings

With parenteral administration of Metamizole Sodium, medical control is necessary (high frequency of allergic reactions, including those with a fatal outcome) and the presence of conditions for anti-shock therapy. Patients with atopic bronchial asthma and pollinosis have an increased risk of developing hypersensitivity reactions. Apply with caution to patients: elderly may lead to an increase in the frequency of adverse reactions, especially from the digestive system; with inflammatory bowel diseases. When prescribing to patients with acute cardiovascular pathology, careful control of hemodynamics is necessary. Use with caution in patients with myocardial infarction, during treatment with cytostatics, chronic alcoholism, burdened allergic anamnesis, blood diseases. Necessary to monitor the picture of peripheral blood (leukocyte formula). When using the drug, the development of agranulocytosis is possible, therefore, if an unmotivated rise in temperature, chills, sore throat, difficulty swallowing, stomatitis, as well as inflammation of the external genitalia and anus is detected, the drug should be discontinued immediately. Subcutaneous administration of the drug is not used due to possible tissue irritation. During the treatment period, the urine may turn red (due to the release of the metabolite), which has no clinical significance.

Side effects

Suppression of hematopoiesis, hemorrhages, hypotension, nephritis, allergic reactions. With intramuscular administration, infiltrates at the injection site are possible.

Contraindications to the clinical use of Metamizole Sodium are given in the Table 8.

Table 8. Contraindications to the use of Metamizole Sodium.

Contraindication		
Increased individual sensitivity to Metamizole Sodium and other pyrazolone derivatives	Attacks of bronchial asthma, rhinitis, conjunctivitis	Blood formation disorders
Liver or kidney failure	Hereditary hemolytic anemia	Abdominal pain of unknown origin
Anemia, leukopenia	Kidney disease: pyelonephritis, glomerulonephritis	Blood pressure, below 100
Polytrauma	Porphyria	Shock

Interaction with other medicinal products

The toxic effect of Metamizole Sodium increases with simultaneous use with other non-narcotic analgesics, tricyclic antidepressants, hormonal contraceptives. The effect of Metamizole Sodium is enhanced by histamine H2-blockers, propranolol (anaprilin), weakened by barbiturates. The analgesic effect of Metamizole Sodium is enhanced by sedatives and tranquilizers (diazepam, sibazone). Metamizole Sodium increases the activity of oral hypoglycemic agents, indirect coagulants, ibuprofen, glucocorticosteroids and indomethacin, the sedative activity of alcohol. When used simultaneously with other nonsteroidal anti-inflammatory drugs, their analgesic and antipyretic effects are potentiated and the likelihood of unwanted side effects increases. When used simultaneously with ethanol, the effect of ethanol increases.

Method of application and dosage. Metamizole Sodium: prescribed intramuscularly and intravenously. The method of administration and dose depend on the severity of the disease and are determined individually. The analgesic effect with intravenous administration is higher than with intramuscular administration. The injected solution should be at body temperature. To prevent a sharp drop in blood pressure, intravenous administration should be carried out slowly. The patient should be in a supine position. Necessary to control blood pressure, heart rate and breathing. The procedure requires conditions for anti-shock therapy. A long needle should be used for intravenous administration.

Control regime of Metamizole Sodium.

Clinical and pharmacological group – analgesics and antipyretics, pyrazolones ATC code N02BB02 [24]. Classification and legal group – general. Nomenclature and legal group – according to a doctor's prescription.

Therefore, seems promising to combine Metamizole Sodium in ampoule dosage form with water-soluble anesthetic (ketamine) active pharmaceutical ingredients and sedative tranquilizers.

General characteristics of the active pharmaceutical ingredient Diazepam

International and chemical names: Diazepam; 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2-one. The gross formula is C16H13CIN2O.

Main physicochemical properties: transparent, colorless, or yellowish-green liquid. Physical and chemical properties: sparingly soluble in water, soluble in alcohol.

The drug Diazepex, Sibazon is in circulation on the pharmaceutical market of Ukraine.

The composition of the solution for injections in ampoules: 1 ml of solution contains diazepam 5 mg; auxiliary substances: ethanol 96%, propylene glycol, polyethylene oxide, water for injections.

Clinical and pharmacological group. Psycholeptic drugs. Anxiolytics. Benzodiazepine derivatives. ATC code N05BA01. Pharmaceutical form – ampoules [27].

Marketing research of the active pharmaceutical ingredient Diazepam

In the Table 9 presented a list of ampoule preparations of the ATC code N05BA01 Diazepam.

Table 9. List of drugs of ATC code N05BA01 Diazepam.

No.	Trade name	Medical form	Manufacturer
1.	Diazepex	Solution for injection 5 mg/ml, 2 ml, No. 5	JSC "Grindex" (manufacturer responsible for batch release, including batch control/testing), Latvia HBM Pharma s.r.o. (all stages of the production process, except for series production), Slovakia
2.	Sibazon	Solution for injection 5 mg/ml, 2 ml, No. 5	LLC Kharkiv Pharmaceutical Enterprise "Zdorovia Narodu" (all stages of production, quality control, series release), Ukraine JSC "Halychpharm" (all stages of production, quality control), Ukraine

The data in the Table 9 shows, that ATC code N05BA01 Diazepam includes two ampoules of preparations. The drugs are produced by Ukrainian and foreign manufacturers in the form of a solution for injections in ampoules.

Subsequently, the registration certificates of Diazepam drugs were analyzed (Table 10).

Table 10. Validity of registration certificates of drugs of ATC code N05BA01 Diazepam.

No.	Trade name	Manufacturer	Registration certificate (RC)		
			RC	Date of registration	RC ending
1.	Diazepex	JSC "Grindex" (manufacturer responsible for batch release, including batch control/testing), Latvia HBM Pharma s.r.o. (all stages of the production process, except for series production), Slovakia	UA/15321/02/01	Unlimited from 22.03.2022	–

2.	Sibazon	LLC Kharkiv Pharmaceutical Enterprise "People's Health" (all stages of production, quality control, batch release), Ukraine JSC "Halychpharm" (all stages of production, quality control), Ukraine	UA/5794/01/01	Unlimited from 22.12.2016	–

Medicinal products in the form of a solution for injections, which include Diazepam, contain 5 mg of the active pharmaceutical ingredient in 1 ml. Two medicinal products registered in Ukraine have an unlimited term of registration. Diazepam is produced by the Ukrainian pharmaceutical manufacturer and the foreign JSC "Grindex".

Clinical and pharmacological study of the active pharmaceutical ingredient Diazepam

Pharmacodynamics

Diazepam is a benzodiazepine tranquilizer. It has an anxiolytic, sedative, anticonvulsant, central myorelaxant effect, increases the threshold of pain sensitivity, regulates neurovegetative reactions.

Pharmacokinetics

After intramuscular administration, Diazepam is absorbed incompletely and unevenly, the maximum concentration is reached after 60 minutes. After intravenous administration in adults, the maximum concentration is reached after 15 minutes and depends on the dose. It is quickly distributed in the tissues of organs, primarily in the brain and liver, passes through the placental and blood-brain barriers. Biotransformed in the liver (50%). Accumulates in the brain, providing a long-lasting and pronounced anticonvulsant effect. Diazepam belongs to the long-acting tranquilizers, the half-life of intravenous administration is 32 hours.

The half-life of Diazepam can be increased in elderly patients and patients with liver disease. In patients with renal failure, the half-life of Diazepam does not change. Absorption of Diazepam when administered intramuscularly may vary, especially when administered into the gluteal muscles. Therefore, this route of administration can be used only in case of impossibility of oral or intravenous administration.

Fields of clinical application and special warnings of Diazepam are given in the Table 11.

Table 11. Clinical application and special warnings of Diazepam.

Application		
Acute anxiety-phobic and anxiety-depressive states	Muscle spasms in neurodegenerative diseases	Premedication in anesthesiology during surgical interventions and complex diagnostic procedures
Eclampsia during pregnancy	Alcoholic psychoses with withdrawal symptoms	Delirium
Status epilepticus	Tetanus	Spinal cord injuries
Lumbago	Cervical sciatica	
Special warnings		
To be used only in medical institutions	Patients with organic disorders of the central nervous system should reduce the initial dose of the drug by two times	High doses of the drug can cause somnolence and loss of consciousness
When treating status epilepticus, one should take	Caution when prescribing the drug to patients who have been	Patients with chronic respiratory failure and chronic

into account the possibility of seizure recurrence	receiving antihypertensive drugs, β-blockers, anticoagulants, cardiac glycosides for a long time	liver diseases should use reduced doses of the drug
In anxiety-phobic or anxiety-depressive conditions, it is not recommended to use diazepam as monotherapy	After a few hours after using the drug, amnesia may occur	Patients should be provided with conditions for uninterrupted sleep of 7 to 8 hours
Dependence may develop	After the occurrence of physical dependence on benzodiazepines, stopping the use of the drug may lead to a withdrawal syndrome	With long-term intravenous use of the drug, treatment should not be stopped suddenly, the dose should be gradually reduced

Recovery of symptoms of insomnia and anxiety

Abrupt discontinuation of Diazepam treatment may cause a rebound phenomenon. It is manifested by an aggravation of the condition followed by a rapid reduction of symptoms (mood changes, anxiety or sleep disturbances, restlessness).

Duration of treatment

The duration of treatment should be as short as possible depending on the indications, but should not exceed four weeks for insomnia, 8-12 weeks for anxiety states. The duration of treatment should be increased only after careful assessment of the patient's condition. Patients should be informed about the initiation and duration of treatment and the gradual reduction of the dose should be explained. In addition, the patient should be warned about the possible occurrence of withdrawal syndrome to reduce the state of restlessness, especially when stopping therapy with the drug. Due to the risk of withdrawal syndrome, it is not recommended to change benzodiazepines with a short duration of action during treatment.

Tolerance

Regular use of Diazepam for several weeks can lead to a decrease in the effectiveness of the action.

Amnesia

Benzodiazepines can cause anterograde amnesia. Anterograde amnesia may occur at therapeutic doses, the risk increases at higher doses. Amnestic effects can be associated with inappropriate behavior.

Special groups of patients

Elderly patients (from 65 years old) and weakened patients need a dose reduction. Due to the muscle relaxant effect, there is a risk of falls and fractures in this group of patients. Diazepam can delay the psychological recovery of patients from the symptom complex caused by the severe loss of a loved one. Diazepam should be administered intravenously with particular caution in the treatment of critically ill elderly patients and patients with cardiac or respiratory failure, given the possibility of apnea and/or cardiac arrest. Simultaneous use of Diazepam with barbiturates, alcohol, or other substances with a depressing effect on the central nervous system increases the risk of circulatory depression or suppression of the respiratory center. It is not recommended to use Diazepam in patients with severe liver failure and organic liver damage. For patients with chronic liver disease, the dose should be reduced. Needs to be taken into account when prescribing Diazepam to children and adult patients from the risk groups (e.g., patients with liver disease or epilepsy patients), that 1 ml of the drug contains 100 mg of ethanol. During the treatment with Diazepam and for 3 days afterwards, no alcoholic beverages can be consumed.

Simultaneous use of alcohol, depressants

Alcohol and other depressants should not be consumed during treatment with Diazepam. Such a combination enhances the clinical effects of Diazepam, including the severe sedative effect clinically associated with the treatment of respiratory or cardiovascular depression. The drug contains

propylene glycol, which can cause symptoms similar to those that occur with alcohol abuse. It is not recommended to use Diazepam in patients with psychosis.

Application in depression

Diazepam should not be used as monotherapy for depression or anxiety. Suicidal tendencies may appear in these patients. Diazepam should be used with great caution in patients with a history of drug and addictive addiction. Such patients should be under strict supervision during treatment with Diazepam. They belong to the risk group of addiction and mental dependence. Diazepam is not recommended for the treatment of primary psychotic disorders.

The ability to influence the speed of reaction when driving vehicles or other mechanisms

Diazepam can reduce the speed of motor and mental reactions. On the day of using Diazepam, you should not drive vehicles and work with mechanisms. Anxiety, amnesia, impaired concentration, and muscle weakness adversely affect the ability to drive and operate machinery. In the case of insufficient sleep and alcohol consumption during treatment, the probability of impaired attention increases. The patient should be warned not to drive vehicles and operate mechanical equipment for three days after taking Diazepam.

Side effects

Long-term use of Diazepam, even in therapeutic doses, can lead to physical and mental dependence. Sudden discontinuation of Diazepam treatment after long-term use leads to a withdrawal syndrome. In order to reduce local reactions, Diazepam should be injected into the large veins of the elbow joint. Intramuscular injection of Diazepam may cause pain, redness, and sporadic tenderness at the injection site.

Violations, lesions, and side effects of Diazepam are given in the Table 12.

Table 12. Disorders, lesions, side effects of Diazepam.

No.	Disorders and lesions	Side effects
1.	General disorders and administration site disorders	Fatigue, general weakness, drowsiness, lethargy, dizziness, headache, slurred speech, confusion, muscle weakness, motor retardation, disorientation, ataxia, accommodation disorder, mood deterioration, decreased attention, increased risk of falls and fractures, phlebitis, phlebothrombosis
2.	From the cardiovascular system	Arterial hypotension, suppression of blood circulation (after rapid intravenous administration of the drug), heart rhythm disturbances, heart failure, bradycardia, rapid heartbeat, in some cases – cardiac arrest, orthostatic collapse
3.	From the respiratory system	Apnea, decreased breathing rate, dyspnea, suppression of the respiratory system (after rapid intravenous administration of the drug), respiratory failure
4.	From the nervous system	Restlessness, excitement, disorientation, visual disturbances (diplopia or blurred vision), drowsiness and muscle weakness, decreased speed of mental and motor reactions, tremor, anterograde amnesia, ataxia, dizziness, headache, catalepsy, asthenia, hyporeflexia, confusion, vertigo, increased or decreased libido
5.	From the mental side	Physical and mental dependence, decreased emotional reactions, depression, speech disorders (in particular, dysarthria), irritability, sleep disorders, aggressiveness, delirium, fits of rage, nightmares, hallucinations (some of sexual nature), psychoses, behavioral disorders, delirium and seizures, suicidal tendencies. Long-term use of the drug (even in therapeutic doses) can lead to the development of physical dependence: stopping therapy can cause a withdrawal syndrome or a rebound phenomenon

6.	From the digestive system	Nausea, xerostomia or excessive salivation, belching, hiccups, constipation, loss of appetite, colic, dry mouth, vomiting, impaired liver function, increased liver enzymes, jaundice
7.	Changes in laboratory parameters	Increased activity of transaminases and alkaline phosphatase
8.	From the urinary system	Incontinence or retention of urine (spastic ischuria)
9.	From the immune system	Allergic reactions in the form of skin hyperemia, skin rashes and itching, bronchospasm, laryngospasm, inactive pharmaceutical ingredient lactic shock, hypersensitivity reactions, including inactive pharmaceutical ingredient lactic reactions
10.	From the musculoskeletal system	Pain in the joints
11.	From the hematopoietic system	Leukopenia, neutropenia, agranulocytosis, anemia, thrombocytopenia, disorders of the morphological composition of the blood, jaundice
12.	From the skin and subcutaneous tissue	Rashes, allergic dermatitis, urticaria
13.	From the metabolism	Metabolic disturbances, including metabolic acidosis, an increase in the size of the anion gap and osmotic hypertension, as a consequence of the toxic effect of propylene glycol

Contraindication

Hypersensitivity to Diazepam, glaucoma, poisoning with alcohol and sedatives, liver failure, acute respiratory failure, alcohol or drug addiction, chronic psychoses, intoxication with alcohol, psychotropic drugs, shock, coma, severe liver failure, phobias, and obsessive states. Diazepam should not be used as monotherapy for the treatment of patients with depression or anxiety because of the potential for suicidal behavior in such patients.

Interaction with other medicinal products

Antipsychotic drugs. There is an increased risk of arterial hypotension, bradycardia, and respiratory depression with parenteral use of Diazepam and intramuscular administration of olanzapine.

Sodium oxybate. Diazepam increases the effect of sodium oxybate.

Antibacterial agents. Metabolism of Diazepam can slow down isoniazid, erythromycin. The effect of Diazepam can be increased and prolonged.

Antiviral means. Simultaneous use should be avoided, as potentiation of the action is observed, the risk of excessive sedation and respiratory depression increases.

Antifungal drugs. The effect of Diazepam can be increased against the background of simultaneous use of fungicides (ketoconazole, fluconazole).

Antihypertensive drugs. The simultaneous use of Diazepam with antihypertensive agents can lead to an increase in the hypotensive effect. Enhancement of the sedative effect is possible with simultaneous use with alpha-blockers.

Medicines that reduce the acidity of gastric juice. Cimetidine, omeprazole, and esomeprazole may inhibit the metabolism of Diazepam.

Disulfiram. Disulfiram can suppress the metabolism of Diazepam, which leads to an increase in the sedative effect.

Levodopa Diazepam can antagonize the effect of levodopa.

Theophylline. Theophylline can reduce the effect of Diazepam.

Skeletal muscle relaxants. The simultaneous use of baclofen with Diazepam can lead to an increase in the sedative effect.

Method of application and dosage. The dose of Diazepam should be determined individually for each patient. Single dose, frequency and duration of use are set individually. Acute anxiety-phobic and anxiety-depressive states. Adults should be prescribed intravenously or intramuscularly in a dose

of 1-2 ml (5-10 mg). With alcoholic delirium, the initial dose is 2 ml (10 mg) intravenously, then 1-2 ml (5-10 mg) every 3-4 hours until the acute symptoms disappear. The highest single dose is 30 mg, the highest daily dose is 70 mg. Status epilepticus: adults are prescribed 1-2 ml (5-10 mg) intravenously slowly. Muscle spasms in neurodegenerative diseases, spinal injuries: adults are prescribed 2-4 ml (10-20 mg) intravenously slowly or intramuscularly. If necessary, the injection should be repeated after 3-4 hours, followed by the transition to taking Diazepam in the form of tablets. Tetanus: the initial dose for adults is 2 ml (10 mg) intravenously slowly or intramuscularly, then switch to intravenous drip administration of the drug at a rate of 5-15 mg/h. Muscle spasms of peripheral origin (lumbago, cervical radiculitis): appoint 2-4 ml (10-20 mg) intramuscularly 1-2 times to adults until the acute symptoms disappear. Then continue the therapy with the drug in the form of Diazepam. Anesthesiology, surgery: for premedication, adults are prescribed 2-4 ml (10-20 mg) intramuscularly the evening before surgery, 1-2 ml (5-10 mg) intramuscularly or intravenously slowly 30-60 minutes before surgery or immediately before surgery. After surgery, enter 1-2 ml (5-10 mg) intramuscularly. To achieve a short-term narcotic sleep during therapeutic and surgical interventions (minor surgical operations, dislocations, fractures, diagnostic measures), adults are administered 2-6 ml (10-30 mg) intravenously slowly.

Overdose with Diazepam

Symptoms: sudden retardation, excessive drowsiness, deep prolonged sleep, nystagmus, apnea, depression of the cardiorespiratory system, excitement, bradycardia, reduced response to pain stimuli, impaired coordination of movements, decreased blood pressure, suppression of reflexes, short-term loss of consciousness, which passes into coma, a fatal outcome is possible. Symptoms of minor overdose: confusion, drowsiness, lethargy, impaired consciousness, reduced reflexes or paradoxical depression.

Diazepam overdose treatment.

If necessary, carry out symptomatic therapy. It is also necessary to ensure the patency of the respiratory tract, control the heart rate, blood pressure, and body temperature. Take measures to maintain the activity of the respiratory and cardiovascular systems. Specific antidote flumazenil (intravenous). Patients requiring antidote therapy are subject to careful monitoring in hospital settings. Flumazenil should be used with caution in patients with epilepsy who are treated with Diazepam. Barbiturates should not be used in case of psychotropic agitation.

Storage conditions: store in the original packaging at a temperature not higher than 5ºC. Keep out of reach of children.

Control regime of Diazepam. Clinical and pharmacological group – psycholeptics, anxiolytics, benzodiazepine derivatives of ATC code N05BA01. Classification and legal group – psychotropic drug. Nomenclature and legal group – by a special doctor's prescription form F-3.

Therefore, Diazepam in ampoule dosage form can be promisingly combined with **water-soluble anesthetics (ketamine) and analgesics (metamizole)**.

We present the composition of the proposed new medicine (Fig. 3).

The proposed composition of the new drug includes two solutions.

The composition of the solution No. 1

Rp: Ketamin 0.002
Aquae pro injectionibus ad 1.0 ml
D.t.d. in ampullis.
S. For anesthesia, during surgical interventions, one ampoule subcutaneously, intravenously, intramuscularly, in droppers!

The composition of the solution No. 2

Rp: Diazepam 0.002
Metamizole sodium 0.25
Aquae pro injectionibus ad 1.0 ml
D.t.d. in ampullis.
S. For sedation, analgesia, during surgical interventions, one ampoule subcutaneously, intravenously, intramuscularly, in the operative and postoperative period!

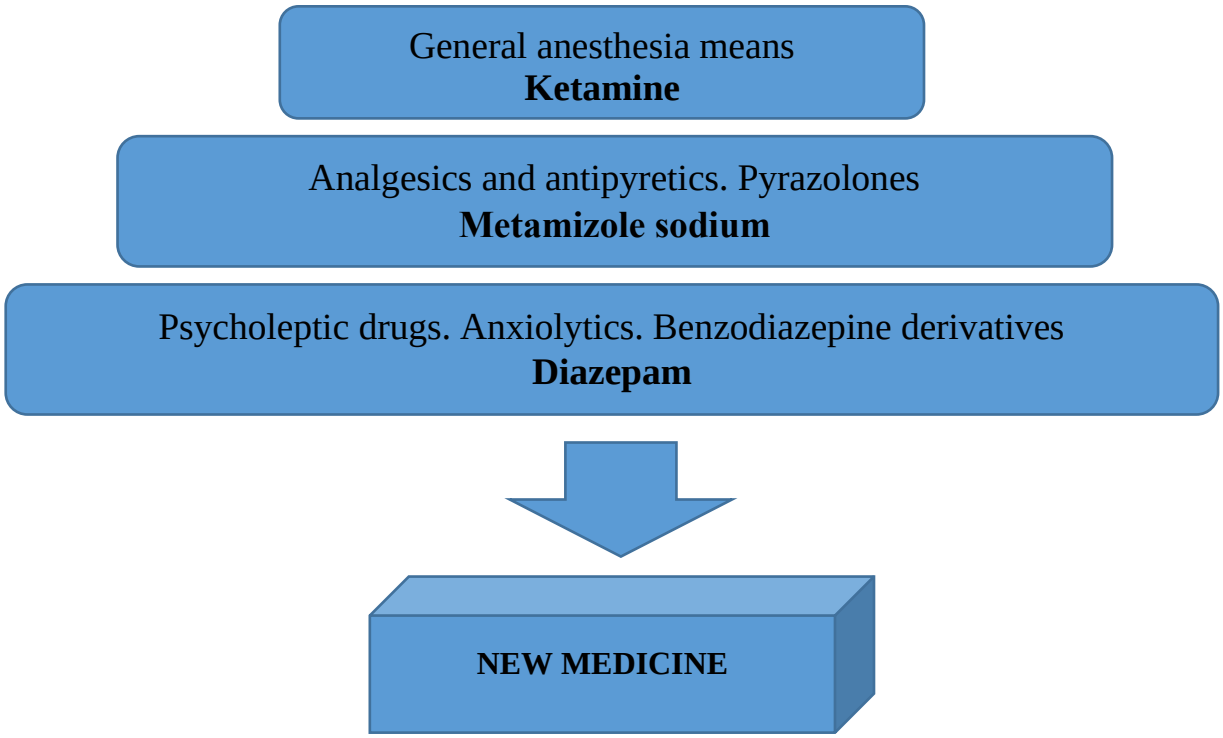

Fig. 3. Clinical and pharmacological groups and active pharmaceutical ingredients in the composition of a new medicine.

Positioning of the control regime of new medicine. The combined medicine contains psychotropic active pharmaceutical ingredients. Solution No. 1 contains Ketamine, a psychotropic active pharmaceutical ingredient whose circulation is restricted. Solution No. 2 contains Diazepam – a psychotropic active pharmaceutical ingredient, the circulation of which is limited and in relation to which it is allowed to exclude some control measures; as well as Metamizoli – an active pharmaceutical ingredient of the general group. Psychotropic active pharmaceutical ingredients are found in both solutions No. 1 and 2 in small quantities, which allows to reduce the measures of the traffic control regime. Classification and legal group of the solution No. 1 is a psychotropic drug. Classification and legal group of the solution No. 1 is a combined medicinal product. Nomenclature and legal group of the solution No. 1 –according to a special doctor's prescription form F-3, subject-quantitative accounting. Nomenclature and legal group of the solution No. 2 – according to a doctor's prescription form F-1, subject-quantitative accounting.

Positioning of the availability of new medicine. The use of a new medicine requires licensing of activities related to the circulation of psychotropic drugs.

Positioning of clinical and pharmacological properties of new medicine. Anesthetic, analgesic, tranquilizing, sedative properties.

Positioning of areas of medical application of new medicine. Traumatology, surgery, psychiatry, neurology, cardiology, oncology, phthisiology.

Indications for medical use. Injuries of the locomotor system Open wound surfaces, painful shock. Surgical intervention in field, military, hospital conditions. Post-traumatic syndrome, depression, comorbid pain, panalgia.

Conclusion. An interdisciplinary study was conducted on the relevance, necessity and timeliness of the pharmaceutical development of a new combined drug for lesions of the musculoskeletal system based on known active pharmaceutical ingredients using clinical, surgical, traumatological, clinical and pharmacological, classification and legal, nomenclature and legal, forensic and pharmaceutical, organizational and legal, marketing approaches to the justification of the composition, clinical and pharmacological properties, control regime, availability, areas of medical application, quality and safety profile. Proven that the use of anesthetic, analgesic, and

tranquilizing drugs is relevant in wartime conditions for medical-pharmaceutical assistance for injuries of the locomotor system in military and civilian persons. The characteristics of active pharmaceutical ingredients (ketamine, analgin, diazepam) were studied in order to substantiate the composition based on a combination of evidence-selected active pharmaceutical ingredients.

Conflict of interest. The authors have approved the article for publication and declare that the research was conducted in the absence of any conflict or potential conflict of interest.

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